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Special Issue on
The Evolving Safety Profile of
rhBMP-2 Use in the Spine

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Editorial

A challenge to integrity in spine publications: years of living dangerously with the promotion of bone growth factors

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- "There were no unanticipated adverse events related to the use of INFUSE Bone Graft." (n=24) Burkus et al. [1] (industry-sponsored study, 2002).

- "[T]here were no complications attributable to the rhBMP-2/biphasic calcium phosphate [in posterolateral fusion]." (n=20) Boden et al. [2] (industry-sponsored study, 2002).

- "There were no unanticipated device-related adverse events [using rhBMP-2 with an anterior cervical fusion]." (n=18) Baskin et al. [3] (industry-sponsored study, 2003).

- "I have reported the clinical and radiographic results of three different interbody constructs in a single-level, stand-alone ALIF derived from several prospective multicenter studies… There were no adverse events due to rhBMP-2." (n=326) Burkus [4] (industry-sponsored studies, 2004).

- "No unanticipated device-related adverse events occurred [with PLIF using rhBMP-2]… This study seems to confirm the safety results …[of] using rhBMP-2." (n=34) Haid et al. [5] (industry-sponsored study 2004).

- "Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy [rhBMP-2]… a 100% fusion rate and no significant morbidity." (n=24) Boakye et al. [6] (industry-associated author).

- "No adverse event that was specifically attributed to the use of rhBMP-2 matrix [Amplify] in the study group was identified." (n=239) Dimar et al. (industry-sponsored study, 2009) [7].

- "Yes, isn't it pretty to think so." Ernest Hemingway, *The Sun Also Rises*.

After the original industry-sponsored trials for recombinant human bone morphogenetic protein-2 (rhBMP-2), which were remarkable for the complete absence of reported rhBMP-2–related clinical adverse events, there came many reports of complications by authors unsponsored by the promoting company [8–13]. With these reports, the

safety profile of rhBMP-2 use has devolved, with troubling rapidity and little introspection about the processes, including idiosyncratic trial design, reporting bias, and peer-review/publication shortfalls, that may have promoted widespread poorly considered on- and off-label use, eventual life-threatening complications and deaths [14].

In this issue of *The Spine Journal*, Carragee et al. [15] present a systematic critical review of the original industry-sponsored trials that assesses how the changing safety profile of rhBMP-2 evolved methodologically and in the publication process. As the review points out, none of the original estimates of safety for any of the rhBMP-2 applications cited above proved accurate. More disturbingly, the published

reports underestimated the risks of rhBMP-2 use despite indications from the earliest trials that inflammatory reactions, adverse back and leg pain events, radiculitis, retrograde ejaculation, urinary retention, bone resorption, and implant displacement may have been problems associated with rhBMP-2 use [2,5–7,16,17]. Serious potential problems, such as the association of rhBMP-2 with sterility or cancer risks, which were prominently discussed in Food and Drug Administration documents and hearings [18,19], did not receive one line of discussion in the industry-sponsored publication of those trials [7,20,21]. The current systematic review found that rhBMP-2–related complications and adverse events, as documented in original Food and Drug Administration reports and subsequent publications, are perhaps 10 to 50 times the original estimates calculated from industry-sponsored studies [15]. Those same studies were published by some authors with tens of millions of dollars of financial associations with the manufacturer and may have been an intrinsic confounding factor [15].

This issue of The Spine Journal also presents a number of original studies that look at adverse effects of rhBMP-2 in spinal fusion and associated issues (Table). The reader may reflect, in reviewing these studies, on how far we have come from the heady confidence of the original reports claiming not a single adverse event associated with rhBMP-2 use in 780 protocol patients.

Conflict of interest and limitations of industry-sponsored trials

The context for this special issue is the remarkable absence of rhBMP-2–associated complications in any of the 13 original trial industry-sponsored publications on this product [15]. It is important for readers to consider in this special issue the evolving understanding of both the biology of bone growth factors and the limitations of our current methods of assessing new technology through industry-controlled clinical trials. Consumer groups and press reports suggest a rising, if not malignant, doubt about the spine field's ability to honestly assess and report on clinical practice and new technologies [22–33]. With regard to the rhBMP-2 issue, the main objection is clear: Authors of nearly all those trials had financial ties with the manufacturer of rhBMP-2, with various compensations ranging to more than 26 million dollars/per study [15].

The range of critics is formidable; from Consumer Reports to The Wall Street Journal, from the Milwaukee Journal Sentinel to the US Senate, from the New York Times to the Department of Justice, and so on [22–33]. These critics suggest that, on balance, some clinical researchers in the current "market environment" cannot be trusted to resist enormous financial forces that encourage biased reporting. The headlines record a near-constant drumbeat of controversy surrounding the promotion of bone growth factors: These range from alleged improprieties of financial disclosure in BMP research [23,27,34]; failing to report likely

complications with rhBMP-2 [22,23,29,35]; publication and research misconduct of BMP trials [24,36–38]; improper representations at US Senate testimony on BMP [39]; allegations of editorial board improprieties regarding BMP manuscripts [27,35,36], and so on. The list continues and is disheartening.

The choirboy defense versus a threat to scientific integrity

Within the spine community, some contend that there is no systematic problem, that is, the "choirboy defense." We are an honest profession; our integrity is unimpeachable; our ethical standards are not in doubt; potential conflicts of interest are only "potential"; the fact that the speaker or author may have millions of dollars riding on device royalties or consulting agreements with the sponsoring company is immaterial; that another author gets millions in royalties from the only on-label approved device for rhBMP-2, could never impair his objectivity in assessing its safety or effectiveness. Outside the echo chamber, however, much of this rhetoric fails to pass the test of minimum credibility.

Instead, the press and public assume that multimillion dollar compensation packages can and do alter the balance of objectivity regarding the fortunes of your sponsor [22–26,28,30,40,41]. And within the medical community, serious doubts have been raised from the Institutes of Medicine to American Orthopaedic Association [42]. Roseman et al. [43] in the Journal of the American Medical Association suggest that skepticism is warranted. They question any topic review or meta-analysis in which the sponsorship and financial association of the authors are not or cannot be assessed as part of the analysis itself. They insist that these relationships are simply a known and powerful source of research bias. Assessment of the literature must include a clear presentation of financial relationships. These are integral to understanding potential biases in study design and analysis. Failure to take these issues into account may lead readers "to trust the conclusions… when they potentially should not" [43]. That is, even within the halls of medicine, many fail to recognize our self-anointed choirboy exemption.

To complicate any attempt at a valid assessment, disclosures in our journals are more often than not self-contradictory blurbs of improbable nonsequitors bracketed by misdirection. For example, a recent article on rhBMP-2 use with posterior spinal instrumentation disclosed: "The manuscript submitted does not contain information about medical device(s)/drug(s). Institutional funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript" [44]. Even the most cursory review shows that this was all about devices and drugs used in an off-label manner and reported by authors who, by conservative

Table
Special issue original articles evolving safety profile of rhBMP-2 use in the spine

Validity of adverse event reporting and bias in the original industry-sponsored rhBMP-2 trials	In a critical review by *The Spine Journal* editors, they found that trial designs may have handicapped the control groups with unnecessary morbidity and long-term clinical failure. Conversely, the reported high ICBG morbidity estimates in these studies were not determined with validated methods. Finally, a review of adverse events as reported in FDA and other documents suggesting the true risk to patients receiving rhBMP-2 is conservatively 10 to 50 times the original estimates calculated from industry-sponsored studies [13]. A complementary study found that large amounts of effective bone graft were potentially discarded in the Medtronic trials of rhBMP-2 in posterolateral fusion, again with potential bias in favor of the rhBMP-2 outcomes [37]
BMP-2 delivery systems and osteolysis	Majid et al. reported on alternative strategies for rhBMP-2 delivery, in part to improve safety. An interesting finding was an increased osteoclast activity in the commonly used adsorption-to-carrier method. This early osteoclast activity is thought to be associated with the osteolysis, bone cyst formation, and subsidence complications now commonly associated with rhBMP-2 use [38]
Osteolysis and complications with PLIF and TLIF surgery	Helgeson et al. reported on extraordinarily high rates of osteolysis after posterior interbody fusion (>50%) and the failure of most of these to resolve over time [39]. Similarly, Mannion et al. examined the rate of radiological and clinical adverse events related to rhBMP-2 in TLIF or PLIF. In a small cohort using a lower rhBMP-2 dosage, adverse events associated with rhBMP-2, namely osteolysis, heterotopic ossification, and cyst formation, were observed in 5 of 30 patients (17%). Complications of rhBMP-2 included cage migration, osteolysis, end plate collapse, and eventual nonunion in one patient and a large inflammatory cyst requiring additional surgery in another. Despite the lower dose and surgical precautions, these events remain a concern [40]
Retrograde ejaculation associated with ALIF surgery and rhBMP-2	A study by Carragee et al. of retrograde ejaculation after ALIF using rhBMP-2 compared with control subjects corroborated the findings of the original FDA data and Smoljanovic et al. that rhBMP-2 may be associated with a higher rate of retrograde ejaculation after ALIF compared with controls (p<.003). These additional data suggest that inflammatory reactions to the rhBMP-2, which have been documented in other locations, may be responsible for an injury to the superior hypogastric plexus when placed anteriorly in the lower lumbar spine [50]
Persistent gluteal pain likely unrelated to iliac crest harvesting	After two recent reports suggesting that the morbidity of ICBG harvesting has been exaggerated in recent industry-sponsored rhBMP-2 literature, Howard et al. reports that patients identified no more pain from the ICBG harvest site compared with the contralateral side at follow-up of more than 1 year [41]. These reports, along with a large body of previous literature, confirm that the 40% to 60% long-term ICBG morbidity rate claimed by industry-sponsored studies is exaggerated [5,42] and consequently exaggerated the potential benefits of rhBMP-2
Neurological injury risks with rhBMP-2	Dimetriev et al. reviewed the rhBMP-2 interactions with the nervous system. They concluded that "contrary to the original beliefs in the clinical community, rhBMP-2 does elicit a profound signaling response within the spinal cord and the peripheral ganglia." Other reports have demonstrated that intrathecal penetration of rhBMP-2 "activates a signaling cascade in all major central nervous system cell types, which may increase glial scarring and impact neurologic recovery" [43]
Dural laceration and rhBMP-2	Glassman et al. [44], in a retrospective industry-sponsored analysis, reports that no clear rhBMP-2-specific neurotoxic effects were apparent when used in the presence of a dural tear. However, the study design limits estimating intradural toxicity events with much precision. The study may indicate that the rate of catastrophic events, when rhBMP-2 is used in the presence of a dural tear, could be less than 5%

rhBMP-2, recombinant human bone morphogenetic protein-2; ICBG, iliac crest bone graft; FDA, Food and Drug Administration; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion; ALIF, anterior lumbar interbody fusion.

estimates, have tens of millions of dollars of financial association with the sponsor [15]. If the disclosure lacks even "minimum credibility," what does this say about the study's content?

The casual reader of the literature is left to wonder how much skepticism is reasonable when reading such an article promoting a commercial product or treatment strategy? Can the reader make any sense of the fine print "disclosures?" Can the reader tell if the authors have a trivial relationship with the industry (eg, the complementary use of the implant during testing) or do the authors receive millions of dollars each quarter from the sponsor? Do the journal editors have

personal multimillion dollar relationships with an articles' sponsor? Was the peer-reviewed process of contrary studies hijacked at the editor level? Although you may wonder, you would not likely be enlightened.

Publication and the editorial review

Clearly, the entire concept of peer-reviewed literature, systematic topic reviews, and evidence-based clinical decision-making rests on the assumption that the published literature being reviewed has sufficient integrity to make

the exercise worthwhile. It is this concept of "sufficient integrity" that has been questioned [45]. In the case of rhBMP-2, 13-peer-reviewed articles by industry-sponsored authors did not report a single adverse event associated with rhBMP-2 [15]. Although theoretically controlled trials should be our highest standard of evidence, it is not necessarily the case: Many of the rhBMP-2 publications either overlooked frequent adverse events or overestimated their statistical power to comment on safety. Instead, Dr Sohail Mirza has characterized the industry-sponsored rhBMP-2 trial designs and publications as a "folly" in multiple dimensions [46].

The rhBMP-2 literature is hardly unique. Gelberman et al. [42] have reported on "the threat to scientific integrity and public trust" associated with the complex financial relationships existing between orthopedic surgeons and the medical device industry. They noted that industry funding in orthopedics is strongly associated with "favorable outcomes." Regarding spinal implant research, they reported a strong pattern of results favorable to the sponsors in approximately three-quarters of the studies. Shah et al. [47] reported an odds ratio of 3.3 favoring industry-supported trials published in the journal *Spine*. The editor of *The Lancet*, Richard Horton, has expressed concerns that in publishing industry-sponsored studies with such a systematic bias to favorable results "[j]ournals have devolved into information laundering operations for … industry" [48]. There have been allegations that editorial conflict of interest in major spine journals has been a fundamental problem as well, with the implication that editorial boards may collude with industry to bring questionable research to publication [27,48].

"As old as scripture and as clear as the American Constitution"

Nonetheless, the rhBMP-2 affair has thrust this issue front and center in spine care. We find ourselves at a precarious intersection of professionalism, morality, and public safety. We work under a burden of suspicion that new technology research and publication is simply a "broken system" as currently practiced [45]. Our professionalism, according to Gelberman et al. [42], is fundamentally challenged by the threat of "tainted science." But as Dr Spengler points out in his important commentary in this issue [49], to maintain our professionalism, we must do more than dress the part or protect compensation: rather the professional obligation of physicians is to "our patients who place their trust in… their surgeons." Dr Spengler suggests that "We must commit to the cardinal rule of primum non nocere (first, do no harm). Our patients remain our number one priority. We need to fulfill their trust."

To change the current climate of suspicion and cynicism, we must look beyond minimal standards of professional conduct or legal compulsion: Beyond the media blitz of the criminal investigations, accusations, and talking-point denials; beyond another set of improbable safety assessments coupled with astounding compensation disclosures; beyond the fortunes found and reputations ruined; beyond any individual or institutional inadequacy that may have permitted these distortions of clinical research. The core of our professional faith, as Spengler points out, is to first do not harm. It harms patients to have biased and corrupted research published. It harms patients to have unaccountable special interests permeate medical research. It harms patients when poor publication practices become business as usual.

Yet harm has been done. And that fact creates a basic moral obligation. As John F. Kennedy stated, "This moral issue is as old as the scriptures and is as clear as the American Constitution." *It is the human right in our society to basic protections*.

In the spirit of that obligation, upcoming issues of *The Spine Journal* will describe a number of editorial-, procedural-, and disclosure-related changes, which we hope will achieve a better balance in critical manuscript review, conflict of interest disclosure, and publication presentation. We all must do a better job going forward.

Author disclosures

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Editorial

Physican-directed (off-label) use of recombinant bone morphogenic protein-2: let us do it well!

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As the entire health-care delivery system in this country comes under increasing pressure to control and reduce costs, the ''off-label'' applications of technology and pharmaceuticals have come under intense scrutiny. This targeting derives from the fact that newly introduced products are more expensive, and there is often a widespread physician-directed use outside of the original Food and Drug Administration (FDA)-approved indication. This wide net of physician-directed use has resulted in significant patient benefit for conditions outside of the original FDA approval. Examples I would cite include the use of lateral mass screw rod fixation for posterior cervical spine fusion and the use of gabapentin for subacute or chronic neuropathic pain syndromes. This wide net of physician-directed use has exposed patients to unrecognized or unpredicted issues or even complications that are undoubtedly drivers of health-care costs as well.

In recent years, recombinant bone morphogenic protein-2 (rhBMP-2) appears to have been assigned the role of the poster child for all that is wrong with ''off-label'' or physician-directed use of a novel beneficial technology. After receiving initial FDA approval for marketing as a specific product and technique that used rhBMP-2 on an absorbable collagen sponge embedded in a titanium-threaded fusion cage for use in anterior lumbar interbody fusion, INFUSE rhBMP-2 (Medtronic, Inc., Minneapolis, MN, USA) was widely used successfully in a host of fusion-related applications. The physician-directed or ''off-label'' use of this product to enhance fusion throughout the spine soon far

outdistanced the approved use. This increased up-front cost along with a virtual monopoly of this product by Medtronic placed this company, its marketing and educational programs, the product, and those who developed it under increased scrutiny and public media sensationalism. The result has been the socioeconomic politicization of a beneficial novel health-care technology.

Adding fuel to this fire was the recognition of adverse events associated with this physician-directed use of INFUSE in the cervical spine. Problematic, even life-threatening swelling with the use of INFUSE in anterior cervical fusions led to FDA warnings [1] and alterations in usage patterns. Intense efforts to determine the cause of these sporadic adverse events have failed to pinpoint the exact cause, but excessive dose of rhBMP-2 appears to be the leading etiology. In the article by Helgeson et al. [2], another associated finding or observation with physician-directed use of INFUSE is reported. Adjacent vertebral osteolysis appears several months after implantation and may persist for years. The clinical significance of this observation is yet unknown as this finding does not appear to have an impact on fusion rate or clinical outcome. The nature or physiologic etiology of this observation is not discussed, but this is not a unique observation, and in other reports, dosage or containment of rHBMP-2 has been implicated.

Outside of this highly charged socioeconomic environment, these observations along with those of exuberant bone formation by Haid et al. [3] and Alexander and Branch [4] in the posterior-threaded fusion cage trial, or heterotopic bone by Branch et al. [5] in a bilateral impacted PLIF trial, would be hailed as significant contributions to the knowledge base driving the indications and ultimate benefit or concern associated with this new technology. Indeed, widespread careful physician-directed use of new technology, with meticulous observation of outcomes and imaging, is the major contributor to the knowledge base for any new technology. Current FDA approval pathways are restrictive and will become increasingly so. Ascertaining the true impact of a new technology or pharmaceutical has been accomplished in the realm of ''off-label'' or

physician-directed use in the past, and this realm of research will have an increasing role in the future.

Physician-directed or "off-label" use of novel technology must be accompanied by careful meticulous physician-directed observation and assessment of patient outcomes. The Achilles Heel of contemporary health-care evidence is the inconsistent or highly variable methodologies of outcome assessment and reporting. Even in the highly controlled military health-care system from which Helgeson et al. reported their observations of osteolysis, only 30% had sufficient follow-up and imaging to be included in this observational report. Although this does not diminish the quality of their observation, little else may be derived from this report. They are building evidence along with others that this is an observation with rhBMP-2 and transforaminal lumbar interbody fusion. Frequency, clinical impact, or etiology cannot be determined from their or others reports.

Industry-sponsored FDA approval pathway studies have been the most meticulous or complete for outcome assessment. Yet, these are limited in scope and now held under suspicion as a consequence of their industry sponsorship. The knowledge base for new technology must be established with prospective, well-designed and executed, and widely implemented studies with imaging and technology intensive outcome assessment and interpretation. Physician-directed use of novel technology should not be prohibited or severely restricted but should be encouraged in the setting of quality outcomes assessment.

It is encouraging to acknowledge that professional societies that shape spine care in this country are collaborating in outcome registry development efforts. A conference in July 2010 organized by Dan Resnick and the Coalition Task Force for Lumbar Fusion [6] brought all of the major participants in this arena together. The FDA, Centers for Medicare and Medicaid Services, United Healthcare, Blue Cross Blue Shield, and spine representatives engaged in a vigorous deliberating on the development of outcome assessment tools and metrics. Human and economic resources are being directed at outcome development from all fronts.

Osteolysis, exuberant and heterotopic bone formation, and cervical soft-tissue swelling represent only a sample of the potential observations associated with the novel rhBMP-2 technology. These observations were made and disseminated by physicians using this technology in an "off-label" or physician-directed indication. The knowledge gained has been invaluable and more is yet to be learned. But the best knowledge or evidence comes from thoughtful, careful, hypothesis-directed investigations with meticulous assessment, and evaluation of outcome. This must be the environment in which we all practice our profession of spine care, especially as we use novel technology and pharmacology for physician-directed indications.

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Review Article

A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned

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Abstract

BACKGROUND CONTEXT: Increasingly, reports of frequent and occasionally catastrophic complications associated with use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal fusion surgeries are being published. In the original peer review, industry-sponsored publications describing the use of rhBMP-2 in spinal fusion, adverse events of these types and frequency were either not reported at all or not reported to be associated with rhBMP-2 use. Some authors and investigators have suggested that these discrepancies were related to inadequate peer review and editorial oversight.

PURPOSE: To compare the conclusions regarding the safety and related efficacy published in the original rhBMP-2 industry-sponsored trials with subsequently available Food and Drug Administration (FDA) data summaries, follow-up publications, and administrative and organizational databases.

STUDY DESIGN: Systematic review.

METHODS: Results and conclusions from original industry-sponsored rhBMP-2 publications regarding safety and related efficacy were compared with available FDA data summaries, follow-up publications, and administrative and organizational database analyses.

RESULTS: There were 13 original industry-sponsored rhBMP-2 publications regarding safety and efficacy, including reports and analyses of 780 patients receiving rhBMP-2 within prospective controlled study protocols. No rhBMP-2–associated adverse events (0%) were reported in any of these studies (99% confidence interval of adverse event rate <0.5%). The study designs of the industry-sponsored rhBMP-2 trials for use in posterolateral fusions and posterior lateral interbody fusion were found to have potential methodological bias against the control group. The reported morbidity of iliac crest donor site pain was also found to have serious potential design bias. Comparative review of FDA documents and subsequent publications revealed originally unpublished adverse events and internal inconsistencies. From this review, we suggest an estimate of adverse events associated with rhBMP-2 use in spine fusion ranging from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects

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reported early back pain and leg pain adverse events; higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy.

CONCLUSIONS: Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications.   © 2011 Elsevier Inc. All rights reserved.

Keywords: Critical review; rhBMP-2 trials; Spinal fusion; Safety concerns; Conflict of interest

Introduction

Spinal fusion techniques have historically used autogenous bone grafting, either from local or distant sources, to augment the local techniques used to stimulate fusion. For long spinal fusions or spinal fusions in adverse metabolic or local conditions, traditional techniques of bone grafting can prove inadequate. Accordingly, bone graft substitutes and enhancers have been developed over time to address these needs. One such bone graft substitute, recombinant human bone morphogenetic protein-2 (rhBMP-2), was introduced commercially in 2002.

There has been an appreciation in the more recent spine surgery literature that frequent and occasionally catastrophic complications are associated with the use of rhBMP-2 in spinal fusion surgeries. Adverse events of this sort were not reported as being associated with rhBMP-2 application in multiple early industry-sponsored trials published in peer-reviewed journals. This article critically reviews the evolving safety profile of rhBMP-2; beginning with the original industry-sponsored publications and progressing to later independent assessments of the product and by independent reassessment of publicly available trial data.

In addition to giving perspective to the specific morbidities of rhBMP-2, it is hoped that lessons can be learned from this era in spinal research and publication. Such lessons might prove valuable in the future, allowing us to better serve not only our community of researchers and clinicians but especially our patients who rely on the expeditious but safe introduction of new technologies in health care.

Summary of events leading to the current review

Multiple studies in the 1990s suggested that bone morphogenetic protein-2 (BMP-2) could cause bone induction in various animal models. There was uncertainty, however, regarding appropriate dosing, appropriate carriers, and safety, all of which appeared to be highly variable depending on the species of animal and location of BMP application [1].

When the use later began in humans, there seemed little doubt that bone induction would be possible; but proper dosing and possible adverse reactions with various applications remained uncertain. Preliminary human trials for lumbar fusion were published beginning in 2000 [2] and 2002 [3]. It was clear at the time that the nature and diversity of adverse events could not be well predicted given that rhBMP-2

appeared to be involved in a multiplicity of physiological and pathological events including, but not limited to, the inflammatory response, bone induction and resorption pathways, abnormal growth signaling pathways, certain malignancy pathways, and induction of an altered immune response [1,4]. Accordingly, in a 2002 review article, Poynton and Lane [4] wrote:

> "Safety issues associated with the use of bone morphogenetic proteins in spine applications include the possibility of bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs."

The results of several small and large industry-sponsored trials were subsequently published [2,3,5–11]. These reported the use of rhBMP-2 in larger numbers of patients undergoing a variety of spinal fusion techniques, including anterior interbody lumbar fusion (ALIF), posterolateral lumbar fusion (PLF), posterior lumbar interbody fusion (PLIF), and anterior cervical discectomy and fusion (ACDF) (Table 1).

Notably, with each new industry-sponsored trial publication, the safety findings were identical: no adverse events associated with rhBMP-2 were reported to be observed. Given that 780 patients received rhBMP-2 in these industry-sponsored publications and that not a single adverse event had been reported, the estimated risk of rhBMP-2 use could be calculated to be less than 0.5% with 99% certainty. That is, the reported risk of an adverse event with rhBMP 2, based on the industry-sponsored data, was less than one-fortieth the risk of a course of commonly used anti-inflammatory or antibiotic medications [12].

Although initially contemplated as an adjunct to spine arthrodesis to be used in particularly adverse clinical situations, a generalized use of rhBMP-2 was observed [13]. In the United States alone, the usage of BMP increased from 0.7% of all fusions in 2002 to 25% of all fusions in 2006, with 85% being used in single- or two-level fusions [14]. By 2007, more than 50% of primary ALIF, 43% of PLIF/transforaminal lumbar interbody fusion (TLIF), and 30% of PLF were reported to use rhBMP-2 [15]. It has been suggested [16] that, at least in part, the documented rapid increase in rhBMP-2 use in spinal surgery was related to the industry-sponsored trials, which reported virtually no

Table 1
Original industry-sponsored or industry-associated author rhBMP-2 clinical studies and reported adverse event rates because of rhBMP-2

Authors	rhBMP-2 Placement	rhBMP-2, n	rhBMP-2 Adverse events (%)	Authors comment regarding rhBMP-2–related observed adverse events in study patients
Boden et al. [2]	Anterior interbody (LT-cage, lumbar, rhBMP-2)	11	0	"There were no adverse events related to the rhBMP-2 treatment"
Boden et al. [3]	Posterolateral (lumbar, ± instrumentation)	20	0	"There were no adverse effects directly related to the rhBMP-2…"
Burkus et al. [5]	Anterior interbody (LT-cage, lumbar, INFUSE)	143*	0	"There were no unanticipated device-related adverse events…"
Burkus et al. [6]	Anterior interbody (bone dowel, lumbar, INFUSE)	[24]‡	0	"There were no unanticipated adverse events related to the use of INFUSE Bone Graft." (2002)
Burkus et al. [39]		79	0	None reported (2005)
Burkus et al. [40]	Anterior interbody (LT-cage, lumbar, INFUSE)	277	0	None reported
Baskin et al. [7]	Anterior interbody (cervical, INFUSE)	18	0	"There were no device-related adverse events"
Haid et al. [8]	Posterior interbody fusion (lumbar, INFUSE)	34	0	"No unanticipated device-related adverse events occurred"
Boakye et al. [41]	Anterior interbody (cervical, INFUSE)	24	0	"Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy…. a 100% fusion rate and nonsignificant morbidity"
Dimar et al. (2009)	Posterolateral (lumbar, INFUSE, pedicle screws)	53	0	None reported
Glassman et al. [42]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	[148]†	0	None reported
Dimar et al. [10]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	239	0	"No adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified"
Dawson et al. [11]	Posterolateral (lumbar, INFUSE, and pedicle screws)	25	0	None reported
Total	All types	780	0	99% CI <0.5% adverse event rate

rhBMP-2, recombinant human bone morphogenetic protein-2; CI, confidence interval.

* Report patients as in Burkus 2003, not included in total rhBMP-2 calculation.

† Possible subgroup of Dimar et al., 2009, not included in total rhBMP-2 calculation.

‡ These patient reported again in Burkus 2005.

complications associated with the use of these powerful biologic products.

In 2002, the United States Food and Drug Administration (FDA) approval was obtained for a single narrow method of spinal fusion: single-level ALIF within specific threaded cages (LT-cage, Medtronic Sofamor Danek, Inc., Memphis, TN, USA). However, over the last 10 years, numerous industry-sponsored articles on rhBMP-2 documented the use for a far wider range of spinal applications. Vaidya [13] summarized the impact of these subsequent publications:

> "We have used it [rhBMP-2] in ways that were not originally approved by the FDA because we felt, if it works so well for one indication; why not try it for others. Many of us read early articles on off label use which showed the results were excellent in the c-spine and in PLIF or TLIF surgery."

Simultaneously, industry-sponsored trials also reported high rates of complications associated with iliac crest bone graft (ICBG) harvesting; the common, practical, and gold standard alternative to rhBMP-2 in most settings. Thus, although complications associated with the rhBMP-2 product were rarely reported, these subsequent publications presented a 40% to 60% morbidity rate with ICBG harvesting [5,8,10].

Beginning in 2006, however, there would be a series of studies detailing serious complications associated with rhBMP-2 use in all settings. Adverse event rates ranged from 20% to 70% in some studies. In June 2008, the FDA issued a Public Health Notification [17] of life-threatening complications associated with rhBMP-2 use:

> "These complications were associated with swelling of neck and throat tissue, which resulted in compression of the airway and/or neurological structures in the neck. Some reports describe difficulty swallowing, breathing or speaking. Severe dysphagia following cervical spine fusion using rhBMP products has also been reported in the literature…. Most complications occurred between 2 and 14 days post-operatively with only a few events occurring prior to day 2. When airway complications occurred, medical intervention was frequently necessary. Treatments needed included respiratory support with intubation, anti-inflammatory medication, tracheotomy and most commonly second surgeries to drain the surgical site [17]."

Shortly after the government safety warning (November 2008), the Wall Street Journal wrote that the US Justice Department was investigating the rhBMP-2 manufacturer, Medtronic Inc. (Memphis, TN, USA), regarding off-label use of the product. The same article also reported three whistle-blower lawsuits seeking damages on behalf of the Federal Government by former Medtronic employees alleging illegal marketing by the company, including "inducements paid to doctors to use Infuse" [18,19]. The Justice Department investigation occurred concurrently with a US Senate Committee investigation into similar issues involving the rhBMP-2 product [18]. Further, a study on rhBMP-2 was retracted from publication by the *Journal of Bone and Joint Surgery [Br]* after allegations of research misconduct and possible fraud by a well-known spinal surgeon [20,21]. It was subsequently reported that the author of the retracted article had extensive, and possibly inappropriate, financial ties with the manufacturer of rhBMP-2 [22].

There has followed in the press an incendiary debate regarding the integrity of and safeguards within spinal research. The media has reported allegations of a wide range of improprieties, including concerns about possible fraudulent data and inappropriate editorial oversight of the rhBMP-2 studies' publication [23–26].

These allegations, particularly the suggestion that this literature has lacked critical editorial oversight from the publishing medical journals, including *The Spine Journal* [24], led the current authors, including the Spine Journal Editor-in-Chief and both Deputy Editors for Evidence and Methods, to perform this systematic review and critical analysis. We reviewed the original peer-reviewed publications of rhBMP-2 trials along with publicly available FDA data and summaries of adverse events possibly associated with rhBMP-2 use for spinal fusion. By comparing these documents, we hoped to independently address whether there were any important omissions, discrepancies, or systematic bias in apparent reporting of possible adverse events between the original industry-sponsored peer-reviewed publications and other available data sources.

Methods

In collaboration with the Reference Desk Services at Stanford University School of Medicine's Lane Library, we conducted a systematic search and critical review of the literature and associated public documents. The electronic library database MEDLINE was systematically searched for literature published from 1995 through 2010 on rhBMP-2 use in spinal surgery. The reference lists of relevant articles as well as primary evidence from government and administrative databases (eg, FDA, Centers for Disease Control and Prevention, and so on) from 2000 to early 2010 were systematically checked and, from these, additional references were added for review. Studies on primary rhBMP-2 use in nonspinal conditions, spinal fusion for

infections, major trauma, rheumatoid arthritis, and other inflammatory joint diseases or tumors were excluded.

From these peer-reviewed articles and associated government and administrative documents, a critical topic review was undertaken. The original industry-sponsored trials were identified and a compilation of adverse events associated with rhBMP2 as published in the peer-reviewed literature by the original authors were assessed (Table 1). The conclusions of these original industry-sponsored rhBMP-2 publications regarding safety and, to a limited extent, efficacy (as influenced by adverse effects) were then compared with available FDA data summaries, follow-up publications, and administrative and organizational database analyses. Although the FDA summaries [27–29] and Public Meeting Documents [30] appear to report on the same trials as appear in some of the peer-reviewed publications, it is not known to us if the authors of the industry-sponsored publications had available or reviewed those FDA summaries, data, or minutes before publication of the peer-reviewed publications.

Adverse events of interest

To avoid the methodological error of analyzing all possible adverse event associations, we confined the comparison of adverse events to those prospectively determined—given the known biology and pharmacology of the rhBMP-2 compound—as being suspect adverse effects before any large trial was reported. As reported by Poynton and Lane in 2002, these were the primary areas of concern:

1. Overgrowth and uncontrolled bone formation
2. Osteoclast activity (graft subsidence, migration, loss of fixation, and so on)
3. Local safety (inflammation, edema, wound problems, and infection)
4. Potential negative effects of BMPs on exposed dura and nerves (neurologic events, retrograde ejaculation (RE)/persistent bladder retention [with ALIF], early back pain, leg pain, radiculitis, and functional loss)
5. Carcinogenicity.

Examining only the prospectively identified, biologically and pharmacologically predicted events reduces the risk of a design error in which chance events are considered real effects simply by the number of possible events analyzed.

Sponsorship and author conflict of interest data

Industry support, financial relationships, and compensation have been identified as potential sources of bias in study design, performance, and publication [31,32]. *The Spine Journal* has required a uniform disclosure procedure, and this was retrospectively applied to all the original rhBMP-2 studies from previously published data provided by the original study authors in *The Spine Journal* [33,34], the Medtronic Physician Registry [35], and other public documents

[26,36]. Roseman et al. [37] have recommended that industry relationships from original publications be clearly presented in systematic reviews or meta-analysis of those studies. Accordingly, these industry sponsorship and author's financial relationships are listed per study in the Supplementary Appendix to provide consistent potential conflict of interest data across a range of studies from different journals.

Statistical analysis

Recommendations of the CONSORT group regarding methods for the reporting of harms associated with clinical trials have been detailed and were followed as the data permitted in this critical review [38]. Statistical analyses of original or comparative data were performed and in most cases conformed to the statistical method used or recommended by the original study authors in their publications (eg, if a one-tailed Fisher test was used in the original study to analyze categorical outcome events, this test was also used in the critical review). Confidence intervals (CIs) were calculated for adverse events in rhBMP-2 and control groups. If there was a compelling methodological reason to use an alternate analysis, these are explained in the text. A set statistical significance for adverse events was not used for reporting harms—after the recommendations of the CONSORT group [38]. Instead for serious or catastrophic events (eg, sterility, neurologic injury, and malignancy) 90% CIs are reported, whereas less serious events (eg, osteolysis without loss of fixation) are reported at a 95% CI. In calculating the maximum estimated adverse event rate from the original peer-reviewed publications, a 99% CI for less than one event in 780 subjects was used. Additionally, the number needed to harm (NNH) was computed to determine the number of patients treated with rhBMP-2 to produce one patient suffering harm because of a specific rhBMP-2–associated adverse event treated (eg, if the risk of a certain adverse event in the treatment group is 10% vs. 0% in the control group, the NNH is 10).

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Systematic review and comparison

The original industry-sponsored trials reported rhBMP-2 use in five primary methods of spinal fusion technique and location. Although there were a number of ancillary publications found with partial data sets, commentaries, and promotional material, there were 10 trials with more complete reporting of an identifiable cohort and outcomes. These were reported in 13 separate articles although some apparent

overlap in study subjects remained. The five study areas included (Table 1):

1. Anterior lumbar interbody fusion using the INFUSE Bone Graft preparation (Medtronic Sofamor Danek, Memphis, TN, USA), which is rhBMP-2 on an absorbable collagen sponge within anterior threaded LT cages (Medtronic Sofamor Danek) or threaded bone dowels with or without supplemental posterior fixation [2,5,6,39,40].
2. Posterolateral lumbar fusion using a lower dose rhBMP-2 or INFUSE/carrier preparation (Medtronic Sofamor Danek) and pedicle-screw and rod implant (Medtronic Sofamor Danek) [3,9,11].
3. Posterior lumbar interbody fusion with an INFUSE preparation and two-paired INTER FIX devices (Medtronic Sofamor Danek) [8].
4. Anterior cervical discectomy and interbody fusion using an INFUSE preparation and an anterior cervical plate (ATLANTIS; Medtronic Sofamor Danek) [7,41].
5. A higher dose rhBMP-2 preparation (AMPLIFY; Medtronic Sofamor Danek) with posterolateral lumbar fusion using Cotrel-Dubousset Horizon pedicle screws and rods (Medtronic Sofamor Danek) [10,42].

Disclosures and conflicts of interest

Each of the 10 original rhBMP-2 trials discussed in the following sections were funded in whole or in part by the rhBMP-2 manufacturer, Medtronic, Inc. Consistent with recommendations by Roseman et al. [37] and *The Spine Journal* disclosure policies, the Supplementary Appendix contains the industry sponsorship and financial disclosures for all 13 peer-reviewed articles and as a range of total compensation for all authors of each study [33–35].

As of March 2011, of the 13 original studies, there was one study with no information available regarding the authors financial relationship with the rhBMP-2 manufacturer. Of the remaining 12 studies, the median-known financial association between the authors and Medtronic Inc. was found to be approximately $12,000,000–$16,000,000 per study (range, $560,000–$23,500,000). For all studies reporting on more than 20 patients receiving rhBMP-2, one or more authors were found to have financial associations with the sponsor of more than $1,000,000; for all studies reporting on more than 100 rhBMP-2 patients, one or more authors were found to have financial associations with the sponsor of more $10,000,000. See Supplementary Appendix.

Part 1: use of rhBMP-2 in PLF

Pilot study

Boden et al. [3], 2002, reported the first randomized controlled trial (RCT) of rhBMP-2 for PLF. This was a small

study with an instrumented ICBG arm (n=5), a noninstrumented rhBMP-2 arm (n=9), and an instrumented rhBMP-2 arm (n=11). The authors reported, ''there were no complications attributable to the rhBMP-2/BCP.'' There were no independent or FDA data sources available with which to compare these findings. However, the early relevant outcomes of the instrumented arms (ICBG vs. rhBMP-2) as reported by Boden et al. were compared. In assessing for local toxicity or neurotoxicity, the early functional outcome, leg pain, and infection rates were compared. The Boden et al. study, in our opinion, gave some indication of possible adverse events associated with rhBMP-2.

During the early period (when the morbidity of the ICBG harvesting should most adversely impact the control group and favor the rhBMP-2 group), it appears there was a strong paradoxical effect toward increased leg pain in the rhBMP-2 group (Fig. 1). Similarly, the early functional outcome (using the Oswestry Disability Index) was inferior in the rhBMP-2 group (64%; 90% CI: 12.5, 60.2; p=.18; Fisher exact test: NNH=2.4) despite the morbidity associated with bone graft harvesting. These data suggested, at an approximately 80% to 90% statistical confidence, that some adverse effect was occurring in the rhBMP-2 group and that this effect was of greater magnitude than bone graft harvesting morbidity. Such an effect might have been related to the known proinflammatory properties of rhBMP-2.

Because the numbers in this trial were small, it is difficult to make firm conclusions on the basis of these data; however, the findings were consistent with pretrial suspicions of possible rhBMP-2–related complications. The larger RCTs of rhBMP-2 formulations used in posterolateral fusions, involving more than 500 subjects (below), would demonstrate this as a consistent effect; there is greater back and leg pain adverse events during the early postoperative period in patients treated with rhBMP-2 compared with control patients exceeding the known expected morbidity of ICBG harvesting [27,32].

Regarding wound problems, in the pilot study by Boden et al. [3] also, there was a 10% rate of wound complications (95% CI, 0–24%; NNH=10) associated with rhBMP-2 use—again suggesting a possible inflammatory effect of the rhBMP-2. This rate of wound complications was significantly higher than the same group's published experience [43] with instrumented posterolateral fusion without rhBMP-2 (p=.03). Later estimates of wound complications in posterior fusion from the Scoliosis Research Society database would indicate an approximately 500% higher rate of both epidural hematoma and wound complications with rhBMP-2 use and a posterior approach [44].

Infuse/mastergraft RCT

Further industry-sponsored RCTs of rhBMP-2 use in posterolateral fusion included many more patients (Table 1), but subsequent authors again did not identify any complications or adverse events related to the rhBMP-2 use [9–11,42,45]. Again, however, both published and unpublished FDA [27] data suggest a consistent paradoxical effect of apparent rhBMP-2 morbidity in the early postoperative period, similar to that seen in the pilot study [3]. Although in each study, the authors hypothesized that there were serious and functionally impairing effects associated with harvesting ICBG, the clinical outcome scores for the rhBMP-2 groups were worse or no better than ICBG group at the 6- to 12-week postoperative time points in all industry-sponsored RCTs on PLF [46].

Dawson et al. [11], in 2009, reported no adverse events associated with rhBMP-2 in an RCT (n=46) of the INFUSE/MASTERGRAFT formulation compared with ICBG in posterolateral fusion. Food and Drug Administration documents published in 2008 [27], regarding the same trial, demonstrated nearly three times as many back and leg pain adverse events in the rhBMP-2 group (vs. controls) during the first 3 months (Fig. 2). At 3 months after surgery, 16% (90% CI: 3.9, 28.0) of the rhBMP-2 group was reported by the FDA documents to have had an adverse event involving back and leg pain compared with 4.8% of the control group (90% CI: −2.9, 12.4).
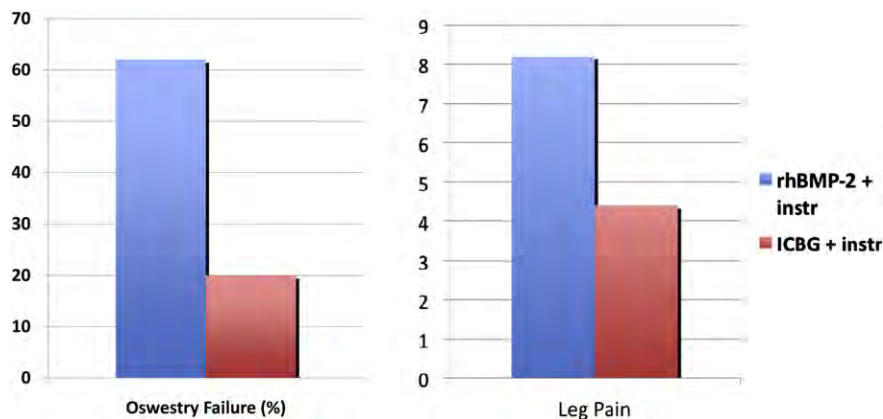
Fig. 1. Six-week postoperative data of early evidence of possible increased functional impairment and radiculitis after posterolateral fusion with recombinant human bone morphogenetic protein-2 (rhBMP-2) compared with control patients [2]. Leg pain is given on a 0 to 20 scale; that is, the leg pain intensity in rhBMP-2 patients was nearly twice that of the control patients.
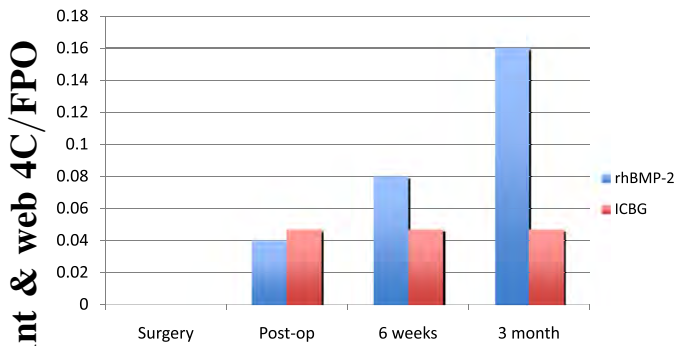
Fig. 2. Early adverse back and leg pain events adverse events (cumulative to the 3 months) after posterolateral fusion using recombinant human bone morphogenetic protein (rhBMP) (INFUSE Bone Graft MASTERCRAFT Granules) compared with iliac crest bone graft (ICBG). Expected outcome of study was less pain in the group without ICBG harvesting, instead paradoxical effect seen of greater back and leg pain morbidity with rhBMP-2 (rhBMP-2 16%, CI: 3.6, 28; ICBG 4.8, CI: −2.9, 12.4; Fisher exact p=.13).

These findings, from more than one RCT, suggest that rhBMP-2 causes equivalent or greater pain and functional impairment than ICBG harvesting in the early postoperative period (strong, Level 1 evidence). This observation was not discussed in any of the published studies despite being evident across multiple RCTs including (and to a larger degree) in the findings of the later higher dose rhBMP-2 study on AMPLIFY [27].

Part 2: use of rhBMP-2 in ALIF

There were five industry-sponsored peer-reviewed publications available on the use of rhBMP-2 in ALIF trials. In the pilot study, Boden et al. [2] reported, "there were no adverse effects directly related to the rhBMP-2…" In 2004, summarizing further industry-sponsored trials of rhBMP-2 use with ALIF, Burkus reported:

> "I have reported the clinical and radiographic results of three different interbody constructs in a single-level, stand-alone ALIF derived from several prospective multicenter studies….There were no adverse events due to rhBMP-2 [47]."

However, careful review of FDA data and subsequent documentation of the largest of these trials suggests osteolysis, subsidence, and adverse neurologic and urologic events were all more commonly seen with rhBMP-2 use.

Osteolysis, subsidence, and reoperation

Smoljanovic and Pecina [48] had noted that abnormal radiographic findings (end-plate resorption, osteolysis, and subsidence) were apparent in the original radiographs (Fig. 3) from the industry-supported RCT publication by Burkus et al. [6] reporting on rhBMP-2 use with bone dowels. That is, the radiograph presented as a model outcome depicts a loss of stability, collapse of the disc space by 50%, and large osteolytic cystic lesions—some extending 50% of the vertebral height. These findings were not commented on/recognized by the authors in the original publication [6]. In a follow-up publication in 2005, Burkus et al. [39] reported on a larger cohort of patients treated with ALIF and bone dowels and again reported no complications, such as end-plate fracture, collapse, and implant migration associated with rhBMP-2 despite the clear radiographic findings in at least the one presented case.

As reported by Burkus in 2004, industry-sponsored trials of ALIF with rhBMP-2 published from 2002 to 2004 found no adverse events associated with its use. However, FDA documents available as early as 2002 had already suggested that some of these findings were evident with those ALIF cases submitted to the FDA during the regulatory evaluation process. The FDA publication "Summary of Safety and Effectiveness Data" [28] concluded the following from the original data:

> "The incidence of adverse events that were considered device related, including implant displacement/loosening, implant malposition and subsidence were all greater in the investigational [rhBMP-2] groups compared to the control group [28]."

This effect was later corroborated in a 2007 nonindustry supported prospective cohort study of rhBMP-2 use in ALIF that found 70% (14 of 20) of levels showed signs of early lucency and more than 10% graft subsidence with a mean collapse of 27% [49]. Another study, this time
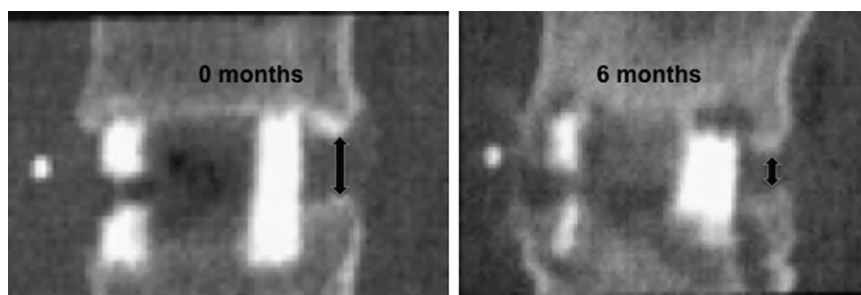
Fig. 3. Computed tomography reconstructions from Burkus et al., showing implant subsidence, disc space collapse (black arrows, 40%), and wide osteolysis (white arrows) with cyst formation extending caudally and around the implanted bone dowel. (From Burkus et al, Spine 2002;27:2396–408, [6], used with permission of publisher; dates and arrows added).

a cohort controlled design, also found greater subsidence and need for reoperation in patients with rhBMP-2 use in an interbody fusion compared with allograft alone [50]. In that study, serial radiographs showed a greater rate of graft subsidence (more than 5 mm) and end-plate failure in the BMP group, all occurring within the first 4 months after surgery. The reoperation rate was higher in the rhBMP-2 group because of revision of graft subsidence complications. These data, again, suggest a clinically important early inflammatory and osteoclastic effect of the rhBMP-2 in soft tissue and bone, respectively.

In a later publication (2009) by the original study group, Burkus et al. [51] appear to contradict the safety conclusions of that group published earlier in 2002 to 2004 [5,6,40,47]. Specifically, a 6-year follow-up study published in 2009 reported again on the original 277-patient cohort discussed above [40]. Here the authors parenthetically reported that there had been seven (2.5%; 90% CI: 0.98, 4.8) early adverse events associated with subsidence in the rhBMP-2 group; but these adverse events were not reported in the original 2-year follow-up study [40]. Subsidence is not at all reported in the 2003 study. Table 2 shows the differences in complication rates reported in the original Burkus et al. study of 2003, the later report by Burkus et al. in 2009, and the original FDA documents available in 2002 [28,40,51].

That is, the authors, in the original 2-year follow-up industry-sponsored publication [40] and summary publication [47], did not report any subsidence or any other specific device-related adverse events; but at 6-year follow-up, more events were reported—and, incongruously, all events were reported to have occurred within the first 2 years [51]. Four of these adverse subsidence events required additional surgery. In fact, 22 additional surgeries for device failure events occurred in the same rhBMP-2 group between 0 and 2 years after surgery according to the FDA summary [28] but were not specifically reported in 2003 or 2004, which were

the same patients over the same time frame. The FDA data [28] reports more complications than either the 2003 or 2009 publications by Burkus et al. [40,51].

Retrograde ejaculation

In the publication of the RCT of ALIF comparing rhBMP-2 against ICBG using the LT-cage, Burkus et al. [5] reported an overall rate of RE of 4.1%. The authors did not report comparative rates of RE in the rhBMP-2 group, nor was this compared with the control arm as was done for other complications. That is, although other complications were reported independently for rhBMP-2 patients and compared with the ICBG patients, the rate of RE was given for the entire cohort without comparison between the two primary study arms.

However, reviewing the same cohort the 2002 FDA Summary of Safety and Effectiveness Data for the use of rhBMP-2 with the LT-cage [28], Smoljanovic et al. [52] noted a higher rate of RE associated with rhBMP-2 use (7.9% rhBMP-2 group, 90% CI: 4.1, 11.6; vs. 1.4% ICBG group, 90% CI: −0.9, 3.8), overall NNH=15, Fisher exact p=.05. This association was not reported in the publication of outcomes from this trial by Burkus et al. in 2002 [5], 2003 [40], 2004 [47], and more recently in 2009 [51].

Later, in response to a Letter to the Editor inquiry, Burkus et al. denied any potential association of this complication RE with the use of rhBMP-2 [52]. They felt that the laparoscopic or transperitoneal approach used in some nonrandomized patients in the LT-cage/rhBMP-2 trial accounted for the excess rate of RE observed with rhBMP-2. However, data reported in FDA documents [28] and further publications [52] confirm that the rate of RE was only slightly higher with laparoscopic insertion of rhBMP-2 containing cages (6 of 62, 9.7% compared with 7.9% in the entire rhBMP-2 group).

Table 2
Failure to report possible rhBMP-2 associated adverse events, complications, and reoperations that occurred during the first 2 years after surgery in the same patient cohorts undergoing ALIF with LT-cage as reported by Burkus et al. in 2003, Burkus et al. in 2009, and the FDA Summary of Safety and Effectiveness

Adverse events type	Adverse events reported by Burkus et al. in 2003 and Burkus et al. in 2004	Adverse events reported by Burkus et al. in 2009	Adverse events reported by FDA in 2002
rhBMP-2 Patients (n)	277	277	277
Early infections (<2 mo)	None reported	None reported	26
Delayed infection (2–12 mo)	None reported	None reported	12
Implant malposition, displacement, and loosening (<3 mo)	None reported	9 (3 required reoperation)	10
Subsidence	None reported	7* (4 required reoperation)	7
Reoperation for device-related adverse event	None reported	7	22[†]
RE	Not reported[‡]	None reported[‡]	12[‡] (7.9%)
Other urogenital AE (mainly retention)	None reported	None reported	36

RE, retrograde ejaculation; AE, adverse event.

* In 2009, seven subsidence events were reported within 6 months of the index surgery, four required reoperation.

[†] Twenty-two of 30 reoperations considered an adverse event related to device "failure" [28,29].

[‡] Twelve events in eleven patients of 140 males from the Burkus et al. rhBMP-2 group, one of 70 males in the control.

Further, the highest level of evidence from the RCT comparing the open use of rhBMP-2 versus autograft (ie, not laparoscopic), observed higher RE rates in male patients receiving rhBMP-2, 6.4% (5 of 78, 90% CI: 1.9, 11.0) than those receiving ICBG 1.4% (1of 68, 90% CI: −0.9, 3.9; NNH=20, p=.14). In both groups, the approach was retroperitoneal in the large majority of cases; the rate of transperitoneal approach was in fact slightly higher in the control group, which had less RE. That is, the rhBMP-2 group had more RE despite a slightly lower rate of transperitoneal approaches. Unfortunately, this finding was not published until 7 years after the original publications [5,6,40], and 8 years after FDA approval of this rhBMP-2 use in ALIF with the LT-cage [28].

Corroborating the finding of an approximately 6% to 7% rate of RE found with ALIF using rhBMP-2, Jarrett et al. [53] reported a 6.4% RE rate (90% CI: 2.5, 10.2) after anterior lumbar surgery, 98% of which used rhBMP-2. However, in ALIF surgery without rhBMP-2, Kang et al. [54], Sasso et al. 2004 [55], and Sasso et al. 2005 [56] reported an RE rate of less than 1% in nearly 1,000 patients, including those followed by FDA protocols. Similarly, Carragee et al. reported a retrospective cohort-controlled study of RE events after lower lumbar ALIF, using an open retroperitoneal approach by a single surgeon [57]. The findings were nearly identical to the eventually disclosed data of Burkus et al.: a 7.2% (90% CI: 2.1, 12.4) RE rate in the rhBMP-2 ALIF patients (n=69) compared with a 0.6% (90% CI: −0.4, 1.5) rate in non-rhBMP-2 patients (n=174). These findings of Carragee et al. were highly significant statistically, indicating a strong association of rhBMP-2 with RE events (Fisher exact test, p=.0025) with a risk ratio of 12.6 and a calculated NNH of 15 (Fig. 4).

In summary, multiple independent studies have found that the rate of RE in ALIF with rhBMP-2 is approximately 5% to 7% and possibly two to four times higher than the rate observed without rhBMP-2. These findings were consistent across multiple studies and designs, including an RCT [28,52], a cohort controlled trial [57], and large observation cohort with more than 1000 patients [52,54].

Urogenital/bladder retention

Other adverse early urogenital events were also more frequently reported in the rhBMP-2 group after ALIF by FDA Summary of Safety and Effectiveness Data: 7.9% of rhBMP-2 (90%: CI, 5.4–10.6) compared with 3.6% of control subjects (90% CI: 1.0, 6.2) and was statistically significant at p=.04 by chi-square test. Although these adverse events (mainly urinary retention after surgery) were documented in the FDA records as associated with rhBMP-2 (Fig. 5), this finding was not reported by the original study authors in their multiple publications: 2002 [5], 2003 [40], 2004 [47], and 2009 [51].

Infections

A ''high'' infection rate (39 infections in 35 of 288 rhBMP-2 patients, 12.2%) was reported in the FDA Summary of Safety and Effectiveness in the rhBMP-2 group of the FDA trial [44]. This finding was not reported in any of the publications by Burkus et al. [5,40,47,51].

Food and Drug Administration documents [28] indicate that early infections (less than 6 weeks postoperatively) were equivalent in rhBMP-2 (9.4%) and ICBG (9.4%) groups. However, delayed infections in the first year after surgery were much more common in patients treated with
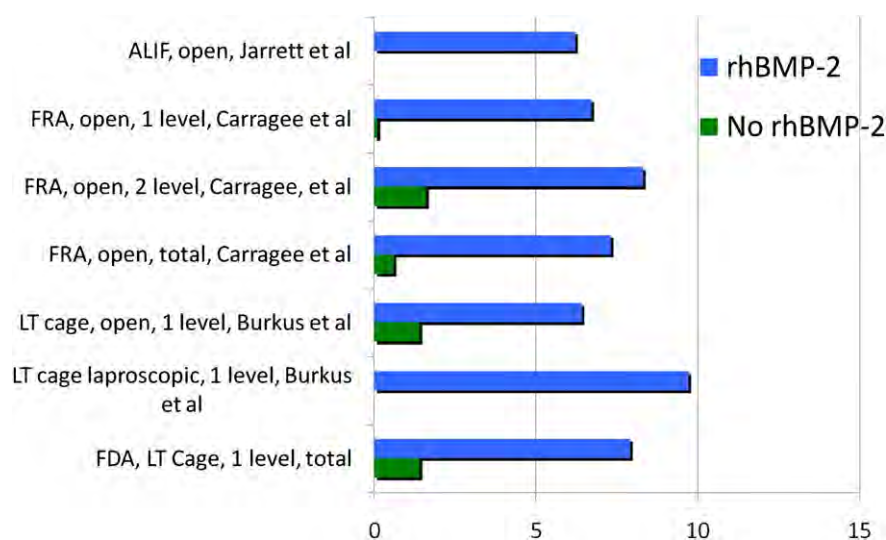
Fig. 4. Comparison of retrograde ejaculation rates (percent) in male patients after anterior interbody lumbar fusion (ALIF) from three studies: ALIF with recombinant human bone morphogenetic protein-2 (rhBMP-2) by Jarrett; femoral ring allograft/rhBMP-2 versus control group (single level and two levels) by Carragee et al., LT-cage/rhBMP-2 versus control (open) group, LT-cage/rhBMP-2 (laparoscopic) group by Burkus et al., and Food and Drug Administration data LT-cage versus control, total cases. See citations in text [28,52,53,57].

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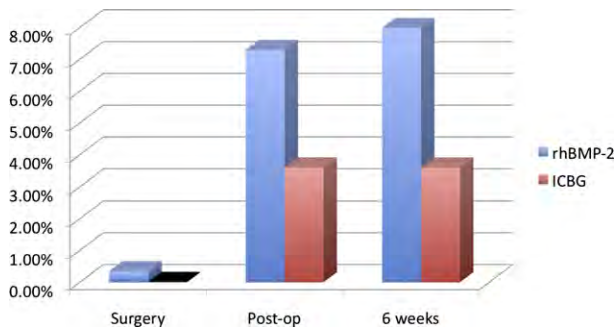
Fig. 5. Cumulative proportion of subjects' urogenital (mainly urinary retention) adverse events after anterior interbody lumbar fusion with LT-cage using rhBMP-2 (INFUSE formulation) versus iliac crest bone graft (ICBG). At 6 weeks rate of this adverse event: recombinant human bone morphogenetic protein-2, 7.9%; 90% CI: 5.4–10.6; ICBG, 3.6%; 90% CI: 1.0–6.2; p=.04 by chi-square test.

rhBMP-2 (12 patients; 4.2%; 90% CI: 2.2, 6.1) compared with the ICBG group (2 patients, 1.4%; 90% CI; −.02 to 3.1); a threefold difference (chi-square p=.07).

Subsequent work from the Scoliosis Research Society has similarly found more frequent deep wound infections in anterior/posterior surgery performed using rhBMP-2 than without. Similar to the FDA data, this was a five times greater rate of infection and highly significant (p=.001) [44].

Part 3: use of rhBMP-2 in PLIF

Haid et al. [8] reported an incomplete industry-sponsored RCT comparing PLIF using rhBMP-2 with an ICBG control. These authors reported, "no unanticipated device-related adverse events occurred." They also reported that no patient required reoperation because of an rhBMP-2 adverse event. They concluded that the study "confirmed the safety" of rhBMP-2 and suggested that the findings might "eliminate the need" for autograft for "successful PLIF." With this presumption of safety, based on 34 study subjects, PLIF and TLIF rapidly became a popular use of rhBMP-2 in the United States: in 2007, 40% to 50% of PLIF/TLIF procedures used rhBMP [15]. On close review, however, several important observations emerge, which were not part of the authors' conclusions.

Bone overgrowth into the spinal canal in the rhBMP-2 group after PLIF

This trial was peremptorily discontinued because of bony overgrowth at the anulotomy site. Computed tomography scan evaluation found new bone formation into the spinal canal or neuroforamina in 24 of 32 rhBMP-2 patients (70.1%; 95% CI: 55.27, 85.91) as compared with four of 31 control patients (12.9%; 95% CI: 11.1, 24.7; NNH=1.6; p=.0001). Although the authors stated that these findings were not associated with adverse outcomes, the curtailed study was not powered to rule out that effect.

Clinical failures in rhBMP-2 group after PLIF

Contrary to expectation, there appeared to be little or no clear clinical advantage in using the rhBMP-2 when compared with ICBG control despite the early morbidity of bone graft harvesting in the control group. At 6 weeks after surgery, there was a 63% greater improvement in the Oswestry score in the ICBG group versus the rhBMP-2 group. Similarly, the global outcomes data at 2 years showed patients were less satisfied with the surgery when BMP was used (Table 3, Fig. 6). The rhBMP-2 group appeared to have more bothersome symptoms, more functional impairment, and less satisfaction (perhaps on an inflammatory basis) than the ICBG group.

The failure to demonstrate clear advantage in the rhBMP-2 group is further complicated by the use of ICBG as the control group. It is now common practice not to use any ICBG in PLIF and TLIF surgeries, but rather to reuse the local bone graft removed to afford access to the disc. Therefore, the Haid et al. data may underestimate the rhBMP-2 relative morbidity compared with local bone graft usage [58–60].

Reoperation in the rhBMP-2 group after PLIF

A surgeon, Dr David G. Malone of Oklahoma, involved in the FDA study reported to the FDA Public Meeting of 2002 that in the experience of his small group with the rhBMP-2/PLIF trial:

"two of the [INFUSE] patients had significant posterior bony over-growth impinging on their nerve roots requiring additional surgery. One patient, who was

Table 3

Global outcomes of patients randomized to undergo PLIF with rhBMP-2 compared with ICBG

	Number	Percent	90% CI
Dissatisfied with surgery			
BMP (n=29)	5	17.24	5.5, 28.8
ICBG (n=30)	1	3.33	−3.0, 9.5
	Difference	13.91	1.1, 27.6
Surgery did help as much as expected			
BMP (n=29)	5	17.24	5.5, 28.8
ICBG (n=30)	1	3.33	−3.0, 9.5
	Difference	13.91	1.1, 27.6
Would have surgery again			
BMP (n=29)	20	68.97	54.8, 83.1
ICBG (n=30)	25	83.33	72.1, 94.5
	Difference	−14.37	−32.4, 3.66

rhBMP-2, recombinant human bone morphogenetic protein-2; PLIF, posterior lumbar interbody fusion; BMP, bone morphogenetic protein; ICBG, iliac crest bone graft.

In all three dimensions measured, the outcomes were perceived as more positive in the ICBG.
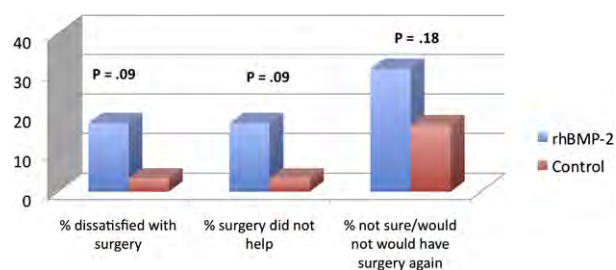
Fig. 6. Patient reported outcomes after posterior lumbar interbody fusion with and without rhBMP-2 from Haid et al. [8]. This industry-supported trial was discontinued with less than 50% enrollment limiting statistical power.

my patient, required two surgeries to clear excessive bone growth from his spinal canal [30]."

This observation was documented in the FDA record years before the Haid et al. study had been published, but these complications were not included in the authors' comments on unanticipated adverse events related to rhBMP-2 in PLIF surgery [8].

It was Dr Malone's opinion expressed to the FDA 2 years before the Haid et al. publication that "BMP may lead to excessive bone growth and may cause significant neural impingement if placed in posterior lumbar interbody type of device." The major adverse events in Dr Malone's patients resulting in reoperation were not included in the Haid et al. article.

Shortly after that Haid et al. publication, when off-label use of rhBMP-2 in PLIF surgery had begun, Wong et al. [61] reported on five patients with ectopic bone formation in the spinal canal after either PLIF or TLIF using rhBMP-2. These patients reported neurological complaints, and three patients underwent an extensive and "difficult" revision surgery [61]. Since then, more reports of serious adverse events associated with rhBMP-2 use in this setting have followed.

Radiculitis, osteolysis, and loss of alignment after PLIF using rhBMP-2

Adverse events associated with rhBMP-2 in PLIF or TLIF are now commonly recognized and are reported to

occur in most patients, including osteolysis and end-plate resorption, increased rates of radiculitis or root injury, cage displacement, subsidence, wound infection, ectopic bone formation, and others [49,62–64]. The most common complications—postoperative radiculitis and osteolysis—have been reported to occur in between 20% and 70% of cases. Others have reported higher rates of subsidence when rhBMP-2 is used compared with other graft methods [49].

Recent close follow-up of the osteolytic defects associated with rhBMP-2 has shown that these findings are common and may result in massive bone loss and relative kyphosis because of collapse (see figures in Hegleson et al. [65] and Knox et al. [66]). Importantly, these defects have been shown to persist in most patients. Hegleson et al. reported that the incidence at 3 to 6 months was 56%; and 76% of these failed to resolve at long-term follow-up [57]. Subsidence of the anterior cage results in a loss of lordosis and relative flat back [66]; a problem associated with poorer outcomes and accelerated superior segment degeneration. At present, several investigators are exploring strategies to limit these complications of the use of rhBMP-2 in PLIF and TLIF approaches. Alternative technical methods (including atraumatic end-plate preparation, applying a sealant to the anulotomy site, and varying the dosage of rhBMP-2) have been suggested [51,54,57,58]; but none, thus far, has proven to be fully successful.

These frequent adverse events might help explain the finding in the original Haid et al. study that more patients in the rhBMP-2 group felt the surgery had not helped and were dissatisfied with the surgery (see Fig. 6).

Part 4: use of rhBMP-2 in anterior cervical interbody fusion

An initial small industry-sponsored RCT of rhBMP-2 in the cervical spine reported no adverse events and, specifically, none associated with the use of rhBMP-2 [58] (Table 4). Boakye et al. in 2005 similarly reported no swelling or wound complications, no reoperations, and no readmissions [41]. Some authors have stated that it was these reported findings coupled with the "perfect" [16] reports from use in other locations that led to more common use

Table 4

Late recognition and reporting of complications associated with rhBMP-2 use in the cervical spine

	Baskin et al. [7]	Boakye et al. [41]	Smucker et al. [70]	Tumialán and Rodts [71]
Patient number (n)	18	24	69	176
Dose per level	0.6 mg	2.1 mg	1.5 mg/ml	0.7–1.05
Dysphagia, n (%)	0	2 (11)	5 (7.2) "severe"	12 (7)
Required PEG placement, n (%)	0	0	1 (1.5)	4 (2)
Readmission, n (%)	0	0	2 (3)	3 (2)
Wound complication, n (%)	0	0	3 (4)	5 (3)
Early reoperation, n (%)	0	0	5 (7)	4 (2)

rhBMP-2, recombinant human bone morphogenetic protein-2; PEG, percutaneous endoscopic gastrostomy.

Although life-threatening events associated with rhBMP-2 use have been reported by the FDA, a precise estimate of excess mortality is not currently available to the public.

in the cervical spine: 13% of all rhBMP-2 use by 2006 and 18% to 20% of all ACDF surgery in 2007 [14,15].

FDA notification of life-threatening complications

In 2008, the Centers for Disease Control and Prevention and the FDA issued a Public Health Notification: "Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine." [17] This Notification followed a number of independent reports specifically noting significant complications when using rhBMP-2 in the cervical spine [67,68]. These included reports of high rates of wound problems, soft-tissue swelling, airway compromise, graft subsidence, and end-plate erosion [49,63,67–70].

Precise data regarding numbers or rate of catastrophic complications and mortality are not publicly available. However, Smucker et al. [70] reported a 27.5% rate of "clinically significant" cervical swelling, which was statistically more frequent than control subjects ($p<.0001$). Even after controlling for confounding variables, there remained a 10.1-fold risk of this adverse event with rhBMP-2 use. Two percent of one author's rhBMP-2 patients required percutaneous endoscopic gastrostomy feeding tube placement because of wound and throat complications impairing nutrition for prolonged periods [71]. Tumialán and Rodts [71] reported a 2% readmission rate and 2% early reoperation when using rhBMP-2, even at a reduced dosage. These figures were similar to Smucker et al., who reported at 1.5% rate of percutaneous endoscopic gastrostomy feeding, 3% reintubation, 4% emergency incision, drainage and decompression of the prevertebral space, and 12% prolonged hospitalization.

Cahill et al. reviewing the National Inpatient Database for acute inpatient complications estimated the adjusted risk of complications to be approximately 40% to 50% higher with the use of rhBMP-2 in anterior cervical fusion than without it. The primary increased events were wound complications, hoarseness, and dysphagia [14].

Osteolysis and loss of alignment

Klimo and Peele [72] reported a 57% moderate or severe osteolysis rate and end-plate resorption with implant migration and loss of sagittal alignment with the use of rhBMP-2 in cervical interbody fusion.

Adverse effects of rhBMP-2 associated with spinal cord injury

Unresolved concerns about the use of rhBMP-2 in the setting of spinal cord injury (and possibly myelopathy) remain—rhBMP-2 appears when penetrating the intradural space appears to adversely impact damaged central nervous system tissue in animal models [73].

Part 5: high-dose rhBMP-2 for posterolateral fusion

The most recently introduced rhBMP-2 preparation proposed for use in the spine is AMPLIFY. This is an rhBMP-2 product with a different carrier and a tripled dose of growth factor (40 mg rhBMP-2 per level) meant for use in posterolateral fusion of the lumbar spine.

The industry-sponsored publication by Dimar et al. [10] compared an RCT of AMPLIFY against an ICBG fusion group similar to that used in previous rhBMP-2 trials of posterolateral fusion (wherein the control included no routine facet fusion, allowed small bone graft volumes, and local bone graft was discarded) [46]. As in previous industry-sponsored trials of this product, the authors reported, "no adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified."

Early back and leg pain morbidity with AMPLIFY exceeds ICBG harvesting

There was no apparent advantage gained from avoiding ICBG harvesting in the first 3 months after surgery given nearly identical back pain, leg pain, and functional outcome scores. This suggests an equivalent morbidity of rhBMP-2 when compared with the bone graft harvesting procedure it is meant to replace [46].

Furthermore, the FDA Executive Summary of this trial published in 2010 [29] identified several classes of serious adverse events, which appeared to be associated with AMPLIFY use but were not reported as such by the Dimar et al. in publication. The summary noted that major back pain and leg pain adverse events, especially early after surgery, were significantly higher in the group receiving rhBMP-2 (Fig. 7, Table 5). There were more than twice as many back and leg pain complications in the AMPLIFY group at both 4 and 8 weeks after surgery (chi-square test $p=.03$). This would represent a complication rate in approximately 12% to 15% of rhBMP-2 patients; more than twice the rate documented in the control group (NNH<15).

Increased risk of malignancy with AMPLIFY

Of additional concern, the FDA found "notably increased cancer rates in the AMPLIFY group." [29] Using the higher dose of rhBMP-2 in AMPLIFY, nine new cancers were diagnosed in 239 subjects; a 3.8% rate (90% CI: 1.7, 5.8) incidence of new malignancy compared with two new malignancies in 224 subjects (0.89%; 90% CI: −0.14, 1.92) in controls (NNH<33, $p=.05$ to 0.1 depending on the statistical analysis), meaning that there is an approximately 90% to 95% probability that this is a real association. This finding was not mentioned in the Discussion section by the authors [10], however, of the 68 pages in the FDA Executive Summary, 15 pages were devoted to the analysis and discussion of the increased cancer issue alone [29].

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Fig. 7. Cumulative early postoperative complications: (Top) Adverse back and leg pain events in the AMPLIFY trial showing a significantly greater increase in major adverse back and leg pain events in patients receiving and not receiving the rhBMP-2 preparation. (p Values, chi-square test, two tail). (Middle) Combined back/leg pain events and arthritis/bursitis events. (Bottom) Serious back and leg pain events in each group.

Although the increased incidence of cancer was a serious enough observation to concern both the FDA and other groups [74,75], the company spokespersons stated that there is "no plausible biological mechanism for cancer induction" caused by rhBMP-2 [76]. However, the basic biology of growth factor signaling in carcinogenesis suggests that categorical denial is not supportable. A theoretical concern regarding malignancy risk with rhBMP-2 was clear when human trials began [4]. In March 2011, the *Wall Street Journal* reported that Medtronic received a "nonapprovable letter" from the FDA for the spine device known as Amplify, "amid outside concerns regarding whether an ingredient used in the product might be linked to cancer" [77].

Part 6: possible study design biases against the control groups

The study designs were examined to consider the possibility of design bias suggested by the media and other observers [23,24,46,78]. We considered whether the choice of fusion technique and ICBG morbidity assessment used in the control groups might have impacted the apparent competitiveness of rhBMP-2 fusion.

Control group technique in the PLF group

The biology of fusion promotion by rhBMP-2 and ICBG is inherently different. The rhBMP-2 product is known to work through bone induction in a variety of tissues and can be anticipated to perform well in a muscle bed, as would be the case of lateral intertransverse process fusion. In contrast, ICBG or other autogenous bone graft acts best locally, where the graft can be contained and packed, to bridge short distances between viable bones, such as a facet fusion. The basic techniques of posterolateral fusion [79,80] and posterolateral fusion with transpedicular fixation [81–83] as originally described include meticulous decortication of the bone surfaces and preparation of the facets. Curettage of the facets, removal of articular cartilage, and impaction of bone graft into the decorticated facet joint are fundamental parts of posterolateral fusion using autologous bone [83], although it may be less important with a primarily osteoinductive agent such as rhBMP-2.

The randomized trials comparing rhBMP-2 with ICBG in posterolateral fusion did not include facet preparation as part of the required surgical protocol but, instead, focused on the intertransverse process fusion. Specifically, the study authors indicate, "fusion of the facet joint was not specifically required by the protocol" [84]. Similarly, when evaluating the fusion radiologically, "the facet joints were not specifically evaluated for the presence of fusion" [84]. As a result, the study design may have biased the clinical outcomes against the ICBG group.

Similarly, the reported rate of radiographic fusion was based on "the presence of bilateral, continuous trabeculated bone connecting the transverse processes." [84] A solid facet fusion alone, often a primary intention of posterolateral fusion when autogenous bone is used, would not be reported as a solid fusion by study protocol.

The study protocols also allowed very small quantities of ICBG to be used as the sole grafting source. The studies indicate that ICBG volumes of as little as 7 cc were used in the control group [10]. At the same time, the local bone graft, which is readily harvested in during the surgery, was discarded. Other studies have shown the volume of local graft available ranges between 10 and 30 cc of bone and in some cases would have been greater than the total ICBG used [85,86]. Discarding local bone graft and failure to prepare facets for arthrodesis are not standard surgical procedures for posterolateral arthrodesis and may have

Table 5
Increased back and leg pain adverse events associated with the higher dose rhBMP-2 (AMPLIFY) used in posterolateral fusion compared with control subjects having ICBG harvesting

Adverse event	Post-op	Wk	Wk	Total	Early %	95% CI
Early back and leg pain		<9 wk				
BMP (n=239)	18	11		29	12.13	8.0, 16.3
ICBG (n=224)	7	5		12	5.36	2.4, 8.3
				Difference	6.78	1.7, 11.9
Early back, leg, and bursitis pain		<9 wk				
BMP (n=239)	21	12		33	13.80	9.4, 18.2
ICBG (n=224)	8	6		14	6.25	3.1, 9.4
				Difference	7.56	2.1, 13.0
Early "serious" back and leg pain events		6 wk	12 wk			
BMP (n=239)	5	1	2	8	3.35	1.1, 5.6
ICBG (n=224)	1	2	0	3	1.34	−0.2, 2.6
				Difference	2.01	−0.7, 4.7

BMP, bone morphogenetic protein; ICBG, iliac crest bone graft; rhBMP-2, recombinant human bone morphogenetic protein-2.
Paradoxical effect of less back and leg pain events in the control group was seen despite the early morbidity of bone graft harvesting.

biased the fusion outcomes against the ICBG control group. Local bone graft has been shown by some to be equally effective as ICBG in promoting fusion in PLF [86,87].

These methodological choices (Table 6) would be expected to result in an increased risk of poorer quality fusion, nonunion, and potential clinical failure when compared with usual recommended practice. Unfortunately, the control used in this and other rhBMP-2 posterior fusion studies does not afford an accurate estimation of arthrodesis rates and final outcomes for the standard method of lumbar fusion using common surgical techniques [46].

Control group technique in the PLIF trial

The PLIF trial used ICBG as the source of autogenous bone grafting. This introduces the short-term morbidity of bone graft harvesting from the ilium, which would have been less or absent if local bone graft had been used alone or supplemented the ICBG in the control group. Before the publication of the industry-sponsored trial of rhBMP-2 in PLIF surgery [8], it had been demonstrated that local bone graft was an effective source of bone for PLIF procedures [60]. Further trials have similarly demonstrated that local bone graft harvested during the approach to the posterior annulus is as effective in PLIF surgery as ICBG [58,59,88]. The use of ICBG in the control may have unnecessarily handicapped the control group. Despite this handicap, there was no clear advantage seen to using the rhBMP-2 and possibly poorer global outcomes in the rhBMP-2 group (Fig. 6).

Table 6
Control (ICBG) fusion in the rhBMP-2 posterolateral fusion trials compared with usual practice for short-segment lumbar arthrodesis techniques: potential bias in rhBMP-2 trials against short- and long-term outcomes of attempted fusion in the ICBG cohorts compared with usual recommended practice

Technique	Usual practice	ICBG fusion method in Infuse or AMPLIFY trials	Adverse effect of methodology on ICBG group outcome
Handling of facet	Meticulous removal of facet joint articular cartilage, joint surface decortication, and impaction grafting	No facet preparation required	Preservation of diarthrodial joint in a prospective fusion segment inhibits fusion rate and stability
Local bone graft	Large quantities of local bone graft (10–30 cc) are often available in degenerative segments to be fused	Discarded	Loss of commonly used autogenous graft in study subjects, increases needed for ICBG dissection and bone harvesting, and if inadequate reduces expected fusion rate and success
Handling of low autogenous bone graft volumes	Augment initial graft harvesting with additional ICBG, local bone, marrow aspiration, or multiple other strategies to increased graft volume and efficacy	No bone graft augmentation even with less than 10 cc of harvested bone available	Using inadequate ICBG, which in quality and quantity would be augmented in usual practice, will artificially lower fusion rates, possibly requiring increased reoperation

rHBMP-2, recombinant human bone morphogenetic protein-2; ICBG, iliac crest bone graft.

Estimates of long-term ICBG morbidity

The industry-sponsored trials made various estimates of morbidity in the control groups from the ICBG harvesting procedures for short-segment fusions. The rate of long-term harm was estimated to be 60%, according to the authors' method of assessment [10,84]. This was substantially higher (50–95% higher) than previous estimates [46,89–91]. The industry-sponsored authors' method of assessment ascribed 100% of any ongoing pain in the region of the iliac crest harvesting to be because of the harvesting alone.

Although this was an unusual assumption at the time, given most spine surgeons experience, subsequent studies have indicated that patients, more than 1 year after surgery, do not perceive more pain on the operative side of ICBG harvesting compared with the opposite side, as determined by two independent investigations [92,93]. That is, patients who have undergone posterolateral fusion of the lumbar spinal, commonly have pain around the site of potential ICBG graft harvesting, whether or not this harvesting was actually performed. Moreover, even when harvesting has occurred, patients cannot reliably discriminate which side had the bone graft procedure.

In summary, compared with the industry-sponsored original estimates of long-term ICBG harvesting morbidity, independent and more rigorous estimates appear to be much lower, if any measurable long-term morbidity can be detected at all [46,92,93]. An overestimation of harm in the control groups from the ICBG harvesting might have contributed to a perceived relative benefit of rhBMP-2 in that clinical situation.

Discussion and conclusion

The availability of rhBMP-2, and other bone graft substitutes, in the treatment of some patients with potential or demonstrated compromised fusion capacity can be a great medical advantage, particularly in patients with long or anatomically deficient fusion beds and other special circumstances.

Recent work by Cahill et al. [94] has shown that use of BMP in single-level lumbar fusion may decrease the need for repeat fusion by 1.1% (ie, at least 100 patients need to receive rhBMP-2 to possibly avoid one revision fusion; NNT=100), with an approximately 10% to 14% increase in costs across all patients. Deyo et al. [95] found no decrease at all in lumbar fusion revision rates after BMP use in older patients. Given these marginal benefits in many patients, the risks of using of a highly potent tissue-signaling drug must be carefully weighed against other options.

As described in the Summary of Events Leading to this Review, there had been wide-ranging allegations of possible underreporting of adverse events in this literature, as well as the suggestion that the original published studies lacked critical editorial oversight from the publishing journals. To critically assess those suggestions, we examined the evidence of whether there were any important omissions, discrepancies, or systematic bias in apparent reporting of possible adverse events between the original industry-sponsored peer-reviewed publication and concurrent or subsequent available data sources.

In this systematic review, we critically assessed the conclusions of authors in 13 published studies regarding the clinical safety and relative efficacy of rhBMP-2 in spinal fusion using CONSORT recommendations for assessing study design and adverse event reporting. Four findings from this review appear clear to us:

1. The estimates of rhBMP-2 safety from the original publications underestimated rhBMP-2–related adverse events of the product. In the small pilot studies [2,3,7], there was inadequate numbers to assess safety, but some suggestion of potential harms was seen in at least one study [3]. In the larger trials, there is evidence in each trial that rhBMP-2 complications may be common and may be serious; but in each publication these were unreported.
2. The presence and magnitude of conflicts of interest and the potential for reporting bias were either not reported or were unclear in each of the original industry-sponsored studies. Some of the conflict of interest statements reported appeared to be vague, unintelligible, or were internally inconsistent.
3. The original estimate of ICBG harvesting morbidity was based on invalid assumptions and methodology. This in turn may have exaggerated the benefit or underestimated the morbidity of rhBMP-2 in the clinical situations tested.
4. The control group methods and technique, as selected for both posterior approach methods (PLIF and PLF), were potentially handicapped by significant design bias against the controls.

As a consequence of these factors, the absolute and relative safety of the rhBMP-2 product was difficult or impossible for readers to ascertain from these original publications. The subsequent reporting of additional studies, the review of administrative, government documents, and subsequent follow-up cohort data have given a fundamentally different picture of morbidity associated with rhBMP-2 use in spinal surgery.

In retrospect, several prominent spine researchers were openly skeptical about the validity of the original publications. Inconsistencies in the data and study conclusions were raised by Smoljanovic et al. soon after the industry-sponsored studies were published. Others questioned the perspective and objectivity of the published presentations. Kahanovitz, commenting on the Haid et al. study, wrote, "Unfortunately, the authors of this study appear to have been overwhelmed by their enthusiasm of using recombinant human bone morphogenetic protein type 2 (rhBMP-2)..." Spengler, former Editor-in-Chief of the *Journal of Spinal Disorders*, commented that he doubted "the (Haid et al.)

article would have been written in such positive terms by authors without financial ties to Medtronic." Others suspected a fundamental bias calling one article "more of a marketing paper than an objective scientific study." [24] At the far end of the spectrum, the complaint from qui tam or so-called "whistle-blower" lawsuits, allege a globally corrupt system of publication and promotion [19,26,96].

However, the nature of this systematic review and the methods and material available preclude any conclusion regarding motive or intent on the part of the original study authors. Rather, as an "after action" learning exercise, a number of points are important to highlight:

- At the inception of human trials of rhBMP-2, it was clear that the nature, range, and frequency of adverse events associated with rhBMP-2 were not fully known. This is usually the case with new drug or device applications. However, as early as 2002, in a review article, Poynton and Lane wrote that safety issues associated with the use of rhBMP-2 might include "the possibility of bony overgrowth, interaction with exposed dura, cancer risk, systemic toxicity, reproductive toxicity, immunogenicity, local toxicity, osteoclastic activation, and effects on distal organs."
- Published trials that should have systematically reported adverse events in the a priori suspect areas did not do so. The evidence for increased early inflammation, back and leg pain events, radiculitis, RE/male sterility, urinary retention, root compression by ectopic bone, osteolysis, and increased cancer rates might have been more clearly recognized and reported via this approach.
- As studies were published from 2000 to 2004, there were no concurrent nonindustry-supported trials available to allow comparison with the reported outcomes of the industry-sponsored trials. Nor were complete data sets made available for analysis by independent reviewers as part of the peer review process. These factors limited the expected external review and analysis expected in high-quality peer-reviewed publications.
- Each of the larger studies, for which independent data could be obtained and reviewed by us, contained findings that could have been considered highly suspicious as direct adverse clinical effects of rhBMP-2 use given the basic biology known a priori; however, these findings were not reported as such in the original publications (See Fig. 8).
- There appears to have been a fundamental error in the statistical analysis of uncommon and serious adverse events within each of the original studies. Three important issues seem deserve consideration:
  - The risk of adverse events should be considered in the context of demonstrated benefits. In trials demonstrating only "noninferiority," in which a specific benefit may be absent (eg, the near identical mean
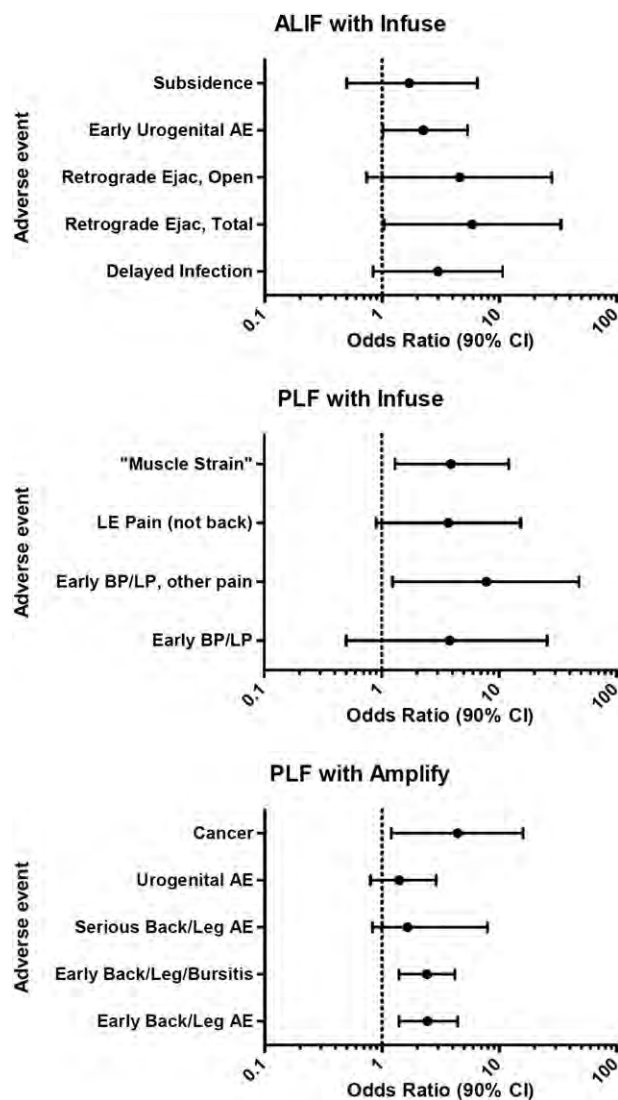
Fig. 8. Odds ratios of adverse events with (Top) rhBMP-2 use in anterior lumbar interbody fusion, (Middle) posterolateral fusion using INFUSE, and (Bottom) posterolateral fusion using AMPLIFY.

clinical outcomes of test and control groups in virtually all these studies), the data analysis must be particularly sensitive to adverse events. These precautions were not observed in these rhBMP-2 publications.
  - The use of an arbitrarily determined and set statistical significance level ($p<.05$) as a criterion to identify possible associations with infrequent (but serious) adverse events is not considered appropriate by CONSORT guidelines [38]. Although noninferiority studies are usually interpreted to protect against Type I (alpha) error (rejecting the null when the null is true), with safety issues, protection against Type II (beta) error (accepting the null when the null is false) should be paramount. With rare events, very large numbers are needed to statistically detect associations at the 0.05 or 0.01 level. To guard against

this, the alpha level should be set higher (eg, 0.1 or 0.2, depending on the seriousness of the event), and CIs computed and shown to reflect that the data are consistent with the possible risk of adverse events. This was not done.

o There was a failure to analyze or report in publication the adverse events occurring during the main pharmacologically active period of the rhBMP-2 drug (weeks). This methodological problem is specifically commented on in the CONSORT recommendation: ''Improperly handling or disregarding the relative timing of the events, when timing is an important determinant of the adverse event in question'' [38]. Instead investigators followed a cumulative event analysis over years of observation, which is more appropriate to monitor long-term device failure. As a result, increased early adverse events such as urinary retention, radiculitis, and severe back pain episodes occurring during the pharmacologically active period were reported. The statistical ''noise'' of random events over years may mask these important and significant complications if considered over an extended follow-up period.

- In those studies for which other data sources have been made available on the same patient sets (either FDA documents or subsequent reporting of follow-up data), serious contradictory findings have emerged. Major complications, additional surgeries, neurologic/urologic injury, and major back/leg pain events were apparently observed but not reported in the original articles. The authors have defended some of this failure to report by citing that their calculated p values did not reflect a 95% or 99% certainty of the effect. However, as described above, in safety assessments, an 80% to 90% confidence of increased risk of cancer or sterility or infections are all clinically significant findings that should have been fully reported in scientific publication.
- By reporting ''perfect'' of ''near perfect'' safety, the original studies might have led others to widespread off-label use of the product with some potentially catastrophic outcomes. With a wider range of reports and data available from both independent and industry-sponsored investigations, a revised estimate of adverse events associated with rhBMP-2 use in the spine can be made (Table 7):

o Posterior lumbar interbody fusion techniques—25% to 50% risk of rhBMP-2–associated adverse events for PLIF techniques including osteolysis, subsidence, graft migration, cyst formation, neuritis, and other events.

o Anterior lumbar interbody fusion—10% to 15% risk of rhBMP-2–associated adverse events including osteolysis, subsidence, graft migration, cyst formation, neuritis, urinary retention, and RE. This

estimate is much higher if a greater requirement for supplemental fixation is included (10% to 15% more).

o Anterior cervical fusion—40% greater risk of adverse events in the acute postoperative period after rhBMP-2 use including potentially life-threatening complications. Food and Drug Administration warnings regarding increased risks of catastrophic complications already exist. Adverse effects on spinal cord injury recovery is highly suspected but not well quantitated.

o Posterolateral fusions with the INFUSE product—an equivalent or greater early postoperative risk of morbidity compared with ICBG harvesting for this dosage; 16% to 20% of rhBMP-2 subjects had adverse back and leg pain events, a probable two to threefold increase in the first 3 months after surgery over control subjects; as well as an undetermined increased risk of wound problems and inflammatory cyst formation.

o Posterolateral fusions with the AMPLIFY product—The high-dose rhBMP-2 preparation in the AMPLIFY product was associated with adverse early back/leg pain and other nonspecific pain events in 14% of subjects, approximately twice as many as control subjects. Similarly, there were twice as many early serious back and leg pain events in the rhBMP-2 group in this period. There remains an unquantified increase risk of neuritis, wound problems, and inflammatory cyst formation. Most importantly, there was a greater rate of new malignancy occurrence in the AMPLIFY-exposed subjects, approximately 90% to 95% probability of this being a true effect.

In conclusion, it is important to consider that identification of problems during the early industry-sponsored lumbar trials may have averted (or at least raised concerns about) complications before significant morbidity and mortality were eventually seen with widespread use. As it was, the presentation of rhBMP-2 morbidity in the original industry-sponsored publications did not fully reflect the data available from those trials as reviewed in FDA documents and subsequent clinical reports.

Instead, we have found that trial design, particularly in the posterolateral fusion and PLIF trials, may have handicapped the control groups with unnecessary early morbidity and long-term clinical failure. Conversely, the reported extremely high-ICBG morbidity estimates in these studies were not determined with validated methods. Finally, retrospective review of complications and adverse events as reported in FDA and other documents suggests the true risk to patients receiving rhBMP-2 is conservatively 10 to 50 times the original estimates calculated from industry-sponsored publications.

Table 7

Summary of complications, morbidity, and mortality associated with rhBMP-2: listed by application (Column 1), as reported by initial industry-sponsored trials (Column 2), and compared with independent assessment of original FDA data, independent assessment of original industry-sponsored publications and subsequent publications of rhBMP-2 (Column 3)

Application	Industry-sponsored original assessment of rhBMP-2–associated adverse events	FDA data and subsequent publication assessment of rhBMP-2–associated adverse events
Posterolateral fusion with rhBMP-2	Boden et al. 2002: "there were no adverse effects directly related to the rhBMP-2…" Dimar et al. 2006: none reported. Glassman et al. 2007: none reported. Dimar et al. 2009: "No adverse event that was specifically attributed to the use of rhBMP-2 matrix in the study group was identified." Dawson et al. 2009: none reported.	Increased risk of malignancy with high doses (eg, AMPLIFY) suspected, (Level 1 Evidence, single RTC); unclear if risk is also elevated in multi-level usage of INFUSE preparation. Morbidity (pain and functional impairment) equal to or exceeding morbidity of harvesting ICBG. (Strong Level 1 evidence, multiple RCT) Increased early back and leg pain adverse events: 16% to 18% with INFUSE, 25% to 30% of patients with AMPLIFY. Two to three times the rate seen in control patients. (Strong Level 1 evidence, multiple RCT) Wound problems: estimates 2 to 5 times rate of problems without rhBMP-2 use. (Level 3 evidence) Sterile cyst formation: rate not clearly defined. (Level 4 evidence) Adverse events associated with dural leak/tear: major/catastrophic events are likely less than 5%. (Level 4 evidence)
ALIF with rhBMP-2	Boden et al. 2000: "There were no adverse events related to the rhBMP-2 treatment." Burkus et al. 2002: "There were no unanticipated device-related adverse events…" Burkus et al. 2002: "There were no unanticipated adverse events related to the use of INFUSE Bone Graft." Burkus et al 2003: none reported. Burkus 2004: "I have reported the clinical and radiographic results of three different interbody constructs in a single-level, stand-alone ALIF derived from several prospective multicenter studies…. There were no adverse events due to rhBMP-2."	Osteolysis, subsidence and implant-loosening/migration: significantly greater than controls. (Level 1 evidence, multiple RCTs, one cohort control study, and at least one observational study) Retrograde ejaculation: 6–9% of male patients. Rate of RE is 2–4 times greater than control patients without rhBMP-2. (p<.05–.01) (Level 1 evidence, 1 RCT, 1 cohort controlled trial, and observational studies all demonstrating similar effect and magnitude of effect) Urogenital adverse events (mainly urinary retention): rate is 100% more frequent than controls. (Level of evidence 2: one RCT, events poorly described) Infections: increased delayed infections with anterior (p=.02) and anterior/posterior (p=.001) procedures using rhBMP-2. Possibly 5 times greater infection rate compared with controls for delayed wound infections. (Level of evidence 2; one RCT, and retrospective review of Scoliosis Research Society database)
PLIF with rhBMP-2	Haid et al. 2004: "No unanticipated device-related adverse events occurred." However, authors admit this trial was discontinued due to bony overgrowth into the spinal canal	Morbidity (pain and functional impairment) equal to or exceeding morbidity of harvesting ICBG. (Level 2 evidence, lower quality RCT) Ectopic bone formation into spinal canal/foramen: approximately 6 times more frequent than control patients without rhBMP-2 (p=.0001) (Level 1 evidence) Osteolysis, subsidence, implant migration, and/or loss of lordosis: found in 50–70% of patients with PLIF and rhBMP-2. Usually does not resolve. Sometimes associated with radiculitis. (Level of evidences 1–2; multiple concordant prospective observational trials, phenomenon highly uncommon without rhBMP-2) Radiculitis because of rhBMP-2 exposure: rate unclear, 2 to 4 times that of control subjects in other studies. Perhaps decreased with sealant at anulotomy. (Levels of evidences 2–3, multiple prospective observational trials, cohort-controlled trials) Global poor outcomes scores: rhBMP-2 patients more dissatisfied with surgery; generalizability uncertain as in one RCT, enrollment stopped before enrollment allowed sufficient power for analysis. (Level of evidence 2, one lower quality RCT) Increased reoperation rate: quantification unclear, FDA data and industry-sponsored reporting are conflicting. See text
ACDF with rhBMP-2	Baskin et al, 2003: "There were no device-related adverse events." Boakye et al, 2005: "Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy….a 100% fusion rate and no significant morbidity."	Increased perioperative mortality. Magnitude is unclear. (Level of evidence 2; confirmed reporting of an exceedingly rare event in the absence of the rhBMP-2 product) Increased perioperative life-threatening events: magnitude is unclear. (Level of evidence 2; confirmed reporting of an exceedingly rare event in the absence of the rhBMP-2 product) Increased perioperative wound problems, difficulty swallowing, impaired vocalization: 40% higher than in patients without rhBMP-2 in acute

Table 7 (*continued*)

Application	Industry-sponsored original assessment of rhBMP-2–associated adverse events	FDA data and subsequent publication assessment of rhBMP-2–associated adverse events
		hospitalization alone. (Level of evidence 2: analysis of large administrative database; multiple small prospective observational studies)
		Prolonged dysphagia requiring tube feeding: 2% of patients even at low-dose formulation: (Level of evidences 3–4, multiple observational studies, one comparative cohort study, large administrative database)
		End-plate resorption, subsidence and loss of alignment: >50% of patients treated with rhBMP-2 (Level of evidence 3)
		Spinal cord toxicity in the presence of cord injury: high-level animal data only at this point (preclinical data)

rHBMP-2, recombinant human bone morphogenetic protein-2; RCT, randomized controlled trial; ICBG, iliac crest bone graft; FDA, Food and Drug Administration; PLIF, posterior lumbar interbody fusion; ACDF, Anterior cervical discectomy and fusion; ALIF, anterior lumbar interbody fusion.

Supplementary material

Supplementary material can be found in the online version at www.TheSpineJournalOnline.com, and at 10.1016/j.spinee.2011.04.023.

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Commentary

Commentary: Resetting standards for sponsored research: do conflicts influence results?

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COMMENTARY ON: Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J 2011;11:471–91 (*in this issue*).

The idea to study biologics to stimulate bone induction remains relevant and of interest to both scientists and clinicians. The original discovery of bone morphogenetic protein (BMP) by Urist [1] in 1965 led to the creation of an intriguing translational research model that ultimately advanced a bench discovery to a bedside application. There was a need for spine surgeons to seek alternatives to iliac crest harvesting for selected patients. For example, in patients who undergo extensive spinal procedures, the iliac crests do not always provide sufficient bone to achieve fusion over a lengthy reconstruction. Allograft and other "fillers" have been used to augment autograft bone, but the success rates to achieve spine fusion using these options have lagged behind the results with iliac crest. As with any new alternative technology, the expectations for scientists, clinicians, and patients would of course include the fundamental premise that any alternative to iliac crest graft must be both effective and safe. The authors of the initial clinical studies that assessed recombinant human bone morphogenetic protein-2 (rhBMP-2) application to the spine did not report any significant adverse effects attributable to rhBMP-2. Over time and with longer follow-up, however, many clinicians have reported serious complications associated with the use of rhBMP-2. Other authors have opined concerns of overlooked adverse events in their review of the original industry-sponsored research [2]. While reporting no complications from rhBMP-2, the authors of the industry-sponsored studies also identified complication rates associated with iliac crest bone harvesting that appeared to be in excess of usual expectations. In an equivalence study where rhBMP-2 was expected to perform only "as well as" autograft bone, a high complication rate associated with the control group (iliac crest graft) would bias results in favor of the rhBMP-2 group.

The systematic review of rhBMP-2 as applied to spine surgery published by Carragee et al. [3] in this issue of *The Spine Journal* offers insight into the sometimes flawed processes that can occur in the development of a clinically applicable biological product. Their careful review was motivated by the spate of complications that have been reported recently and conversations with spinal surgeons who have experienced unexpected complications with the use of BMP-2. Carragee et al. have carefully supported their systematic review. The result is a thoroughly documented treatise that reviewed the initial experiences with rhBMP-2 both from the perspective of the original trial authors and by Carragee et al.'s own interpretation of the data contained within the 13 industry-sponsored studies. Their goal was to formulate the review in such a way as to identify "teachable moments" to be learned from analyzing information that might have been overlooked initially and may have become clearer with the benefit of hindsight. Such information will be useful to future investigators and Federal Drug Agency (FDA) consultants when considering new applications. Most importantly, such information will be of vital importance to our patients who place their trust in the decision analysis skills of their surgeons.

The story of rhBMP-2 unfolds as a fascinating study of a biological product that was classified as a "device" by the FDA because the original approval to use BMP in humans was linked to a collagen carrier and tapered cage. The on-label approval for rhBMP-2 in 2002 was specifically limited to an anterior lumbar approach to perform an interbody fusion

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(anterior lumbar interbody fusion). Bone morphogenetic protein was known to induce bone formation in both a bone environment and in soft tissues [1]. Additionally, BMP was capable of kindling a variety of other physiological events to include an inflammatory response, resorption of bone through the stimulation of osteoclasts, growth signaling pathways (normal and abnormal), malignancies, and induction of an immune response. Safety, with the use of rhBMP-2 in humans, was discussed in an article by Poynton and Lane [4] in the same year as FDA approval. Now some 9 years later, Carragee et al. have concluded that the adverse event and complication rates in patients who received rhBMP-2 for spine surgery were some 10 to 50 times greater than the original estimates from the industry-sponsored peer-reviewed studies.

As clinical experience with the use of rhBMP-2 in spine surgery grew, a number of industry-sponsored studies were published in peer-reviewed journals that cited no significant adverse events in the first 780 patients [3]. With the increasing comfort conveyed by this information, the number of spine fusions augmented by rhBMP-2 soared from 0.7% in 2002 to 25% in 2006 [5,6]. Additionally, the off-label use of BMP expanded to nearly 73% of the total use by 2007 [7]. Such use included posterior lumbar interbody fusions, transforamial lumbar interbody fusions, posterolateral lumbar fusions, and use in anterior fusions for the cervical spine. Any use other than anterior lumbar interbody fusion was considered off label. As the off-label use increased, so did the complication rate. In 2008, the Centers for Disease Control and the FDA published a warning (Public Health Notification) for potential life-threatening complications associated with the use of rhBMP-2 in the anterior cervical spine secondary to severe cervical swelling and other wound-related complications [8].

Although the adverse events and complications associated with rhBMP-2 are well documented in Carragee et al.'s article, I would like to highlight the more significant complications that have been associated with the use of rhBMP-2 as an adjunct to spine surgery in both on-label use and off-label use. These complications include increased wound infection rate, increase in epidural hematomas, and other wound complications, an increased rate of retrograde ejaculation, bony overgrowth in the spinal canal and/or neural foramina, osteolysis with loss of implant alignment, and a suggestion that cancer may be increased in patients who received rhBMP2 versus controls [3].

After reviewing the article by Carragee et al., several questions need to be answered to fully interpret this information. Although I do not have the answers, I believe that we as spinal surgeons must reflect on this well-documented systematic review and do our best to minimize further adverse events and complications associated with rhBMP-2 and to avoid repeating this experience with other products in the future. Although we will always be interested in and supportive of new technology, we must commit to the cardinal rule of primum non nocere (first, do no harm). Our patients remain our number one priority. We need to fulfill their trust.

One area of concern that was raised in the review by Carragee et al. includes the adequacy and effectiveness of our peer review and editorial process. Why were signs of radiolucent zones and implant collapse not noted through the rigors of our peer-review process but raised by readers based on the same images? Some of the other questions that I believe important to pursue after reflecting on Carragee, Hurwitz, and Weiner's manuscript focus on the issue of conflict of interest. Most of us are conflicted in one way or another as we develop experience within our field of expertise. Additionally, we also have conflicts of commitment (eg, investigator, author, reviewer) because we have multiple responsibilities in addition to our patient care mission. We know that carefully run clinical trials require considerable resources, including personnel and financial support. Can we in fact carry out quality-controlled prospective studies without industry sponsorship when we evaluate an expensive implant and/or biological product? Millions of dollars may be required to complete these studies. Where will we find support?

When we do participate with industry on a project are our policies for disclosure of conflicts sufficient in our role as investigators? As authors? As editors? As reviewers? Should we be required to detail the precise amounts of money that we received to perform a study and any consultancy fees or royalties?

Should the off-label use of devices and biologics be more carefully regulated? Certainly, in the rhBMP-2 review, we can recognize the significance of unintended outcomes. Finally, can we really endorse widespread acceptance of a given pharmaceutical or device based only on industry-sponsored studies? Must we require additional independent investigations by individuals and centers that have no conflicts with the device or agent in question?

This is not an easy ground to navigate. We must find the proper balance between the expeditious use of a potential game-changing discovery versus the risks of overlooking adverse outcomes or totally unintended consequences that may occur with a more rapid approval process. This conversation is ongoing with the FDA and new drug releases for the treatment of various cancers.

In summary, I believe that Carragee, Hurwitz, and Weiner have made a most valuable contribution to our field of spine surgery. They have framed the issues and questions. It is now our opportunity to respond. Long-term improvement in our management of new technology and supervision of clinical trials will result.

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Commentary

Commentary: Folly of FDA-approval studies for bone morphogenetic protein

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"To qualify as folly, … the policy …must have been perceived as counter-productive in its own time, not merely in hindsight… a feasible alternative course of action must have been available… the policy in question must be that of a group, not an individual …"

(Tuchman BW. The march of folly: from Troy to Vietnam. New York, NY: Ballantine Books, Alfred A. Knopf, Inc., 1984:5 and 6).

Carragee et al. [1] provided an insightful systematic analysis of the science leading to widespread use in spinal fusion surgery of a biologically active protein, bone morphogenetic protein (BMP). They compared data published in 13 original articles describing the BMP regulatory approval studies with data provided in the US Food and Drug Administration (FDA) Web sites and data reported in the spinal literature by other investigators [2–14]. Their conclusion is well supported by rigorously referenced evidence: the 13 seminal publications systematically aligned research factors to favor results for BMP (Fig. 1).

Qualifying as folly

How could this happen? The FDA's premarket approval (PMA) process for new drugs and devices includes review of study design, study conduct, results, and product labeling.

However, regulators perhaps assumed that there was little risk of intentional or unintentional bias. The US Food and Drug Administration summaries of PMA data are publically available but difficult to access and understand. Clinicians generally receive this information through scientific forums, relying on professionalism of investigators and peer review to ensure scientific integrity. The BMP-PMA studies were reported by some of the most influential names in spinal surgery, but perhaps we rely too much on "thought leaders" and believe too much in magic molecules for overcoming biological limitations. The articles were published in respected scientific journals, but perhaps reviewers and editors compromised respect for research principles with rush for innovation. Practicing surgeons, hospital safety and quality officers, and payers, all sophisticated in their own ways of evaluating science, enabled widespread BMP use and missed the caution now made clear in Carragee's article—biased research placed patients at risk for harm without clear compensatory benefit.

Alignment of bias for systematic error

Open-label study

The BMP-PMA studies were open label. Participating surgeons, patients, and researchers knew the treatment assignment for each subject, enabling conscious and unconscious bias to potentially skew perceptions and judgments. It is hard to avoid bias when comparing surgery to nonsurgical treatment. However study designs with blinded subjects and researchers may be a way to avoid such bias. Studies that compare surgical techniques, study designs that blind subjects and researchers are an option.

Noninferiority trial design

The BMP-PMA studies were designed as noninferiority trials, without the expectation to show better efficacy than

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Problems with BMP FDA Premarket Approval Studies **Direction of Bias**
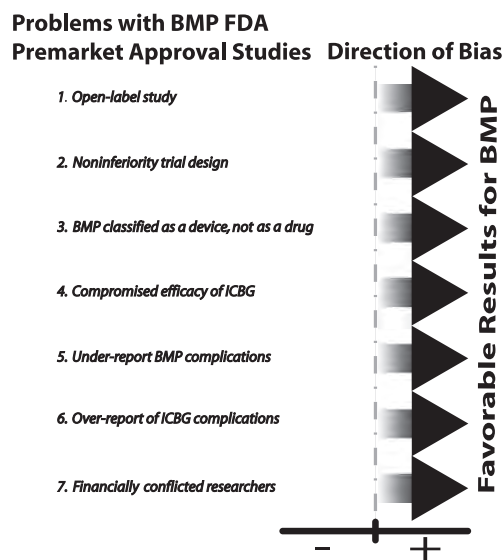
Fig. 1. Limitations in the design and reporting of BMP premarket approval studies aligned bias to uniformly favor BMP. BMP, bone morphogenetic protein; FDA, US Food and Drug Administration; ICBG, iliac crest bone graft.

Fig. 2. A noninferiority trial research design assumes that prior knowledge exists to show the control intervention "C" (eg, fusion) is more efficacious than placebo "P" (eg, nonoperative treatment). The Fritzell study would estimate nonoperative treatment as possibly "P"; however, Brox and Fairbank studies would estimate nonoperative treatment efficacy as "P2," which would make a noninferiority design inappropriate for bone morphogenetic protein fusion surgery to treat back pain associated with disc degeneration [15]. T=efficacy of treatment; C=efficacy of control; P=effect of placebo; M=noninferiority margin (C–T) within which the treatment is specified as equivalent to control, alternatively defined as a percentage of the preknown benefit of control over placebo (0.xx [C–P]). Placebo=condition where control is proven effective over placebo. An example in back pain research is the Fritzell study (2001) that showed lumbar fusion to be more effective than unstructured rehabilitation. Given this prior knowledge, a noninferiority trial would be designed to show that the new treatment is not inferior to control by margin M but is still more effective than placebo by xx%. Placebo 2=condition where control is not effective over placebo, and a noninferiority trial is not appropriate. In back pain research, an example is comparison of lumbar fusion to structured rehabilitation as in the Brox and Fairbank studies.

control. Noninferiority trials are considered when a control intervention has well-established efficacy and the disease being studied has a natural course that makes withholding this efficacious control treatment unethical [15]. Such is not the case for lumbar fusion as a treatment for chronic back pain associated with disc degeneration or "discogenic back pain" (Fig. 2). Efficacy for fusion in relieving back pain is limited, with one trial showing advantage for surgery compared with routine nonsurgical care [16] and three trials showing no advantage compared with structured rehabilitation [17–19]. Benefit with fusion was roughly the same in all four trials. The difference was the benefit from nonoperative care (Table and Fig. 3). Structured rehabilitation yielded improvements similar to fusion [17–19]. No improvement was seen with continuing unstructured nonoperative care that had already failed before enrollment [16].

The natural course of chronic discogenic back pain is not so destructive that withholding surgery would impose harm on the control subjects. Additionally, a noninferiority trial assumes that other benefits, such as lower cost or improved safety, of an experimental treatment offer advantages over potentially more efficacious control treatment. Bone morphogenetic protein is expensive. Better efficacy justification for BMP would require a superiority trial; better safety justification would require an accurate assessment of complications. Carragee et al. proved that these goals were not met by the BMP-PMA studies.

Evaluating BMP as a device, not as a drug

Bone morphogenetic protein is a biologically active protein with local and systemic pharmacological effects during the early period after implantation. Yet, it was tested in the PMA studies as a device and not as a drug. The

FDA-approval process for devices is less rigorous than drugs. Furthermore, the longer time frame essential for evaluating device failures may dilute significance of early adverse events associated with pharmacological actions, such as edema, swelling, pain, radiculitus, urinary dysfunction, and sexual dysfunction. Both these factors biased PMA study analyses to favor BMP.

Compromised efficacy of the control treatment

Carragee et al.'s analysis shows that the control intervention was not delivered optimally in the BMP trials. Lumbar arthrodesis in control subjects did not require decortication or arthrodesis of facet joints. Also, locally removed bone from decompression was wasted. Instead, iliac crest bone graft was harvested, leading to additional morbidity.

Under-reporting of complications in the experimental treatment group

The 13 seminal BMP publications under-reported BMP complications compared with information on the FDA Web site and unsponsored studies. Carragee et al. showed

Table
Change in the Oswestry Disability Index reported in randomized trials of lumbar fusion, bone morphogenetic protein, disc replacement, and nonoperative treatment for chronic back pain [16–19,23,24]

Study	Nonoperative		Fusion		Disc replacement	
	Baseline (SD)	Final (SD)	Baseline (SD)	Final (SD)	Baseline (SD)	Final (SD)
Brox et al. 2006 (Pain) [17]	45 (9)	32 (19)	47 (9)	38 (20)		
Fairbank et al. 2005 (BMJ) [19]	45 (15)	36 (21)	46 (15)	34 (21)		
Fritzell et al. 2001 (Spine) [16]	48 (12)	46 (16)	47 (11)	36 (18)		
Brox et al. 2003 (Spine) [18]	43 (13)	30 (20)	42 (11)	26 (16)		
Blumenthal et al. 2005 (Spine)* [23]			52 (15)	31 (22)	51 (13)	26 (22)
Zigler et al. 2007 (Spine) [24]			63 (10)	40 (24)	63 (13)	34 (25)

SD, standard deviation.

Large SDs indicate wide variation in patient-reported function; SDs at follow-up were generally double those at baseline.

* Score and/or SD measured from published figures.

that the complication rate of BMP fusion procedures is closer to 5% to 15% for anterior procedures and 25% to 50% for posterior procedures rather than the 0% rate reported in the seminal publications.

Over-reporting of complications in the control treatment group

Carragee et al. showed that BMP publications over-reported complications for iliac crest bone graft donor site;

Fig. 3. Change in the Oswestry Disability Index reported in randomized trials of lumbar fusion, disc replacement, and nonoperative treatment for chronic back pain [16–19,23,24]. Higher score indicates greater disability, open points represent baseline ODI, closed points represent post-treatment ODI, and dotted lines represent standard deviation for each. Change from baseline to follow-up is similar for fusion in all trials. Key difference is in nonoperative care: The Fritzell study showed no change, whereas the structured rehabilitation trials showed gains similar to the fusion patients. Baseline scores showed greater disability in the artificial disc trials, where Oswestry Disability Index at the end of treatment was similar to baseline scores in the European trials.

a rate of 60% is too high. A large volume of prior research estimates this number to be between 3% and 30%. Although inflating control treatment complications and deflating experimental treatment complications increase study power for detecting a difference (Fig. 4), a randomized trial is not optimally suited for comparisons of therapeutic safety [20]. Discerning differences in complication rates requires more subjects, longer surveillance, and more realistic clinical conditions than practical for most randomized trials [20].

Financially conflicted researchers

The BMP-PMA studies were funded by Medtronic. Medtronic began reporting payments to physicians in 2010.

Fig. 4. $n = \dfrac{(Z_\alpha + Z_\beta)^2 * \dfrac{R+1}{R} * p(1-p)}{(p_1 - p_2)^2}$. Sample sizes required to detect differences in frequency of adverse events (adapted from Ref. [20]). To detect a difference of a complication rate of 1% in the control group and 5% in the treatment group, with 5% chance of "alpha" or type I error ($Z\alpha = 1.96$) and 10% "beta" or type II error (90% power, $Z\beta = 1.28$), each arm of the study would require 382 subjects. n = Number of patients in the treated group; $Z\alpha$ = "alpha error," quantifies the probability of finding a relationship between treatment and the occurrence of an unfavorable outcome when none is truly present; $Z\beta$ = "beta-error," quantifies the probability of failing to find a relationship when an effect of a specified size is actually present; R = ratio of control subjects to treated subjects; p_1 = cumulative probability of an unfavorable outcome in the control group; p_2 = cumulative probability of an unfavorable outcome in the treated group; and $p = \dfrac{p_2 + R * p_1}{1 + R}$

All 13 articles (100%) contained authors who received payments in 2010. Whether payments were similar during the study periods or whether they started some time after the publications, both constitute strong financial conflict of interest. Carragee et al. estimated that the median payment to authors was $12 million for 12 of the 13 studies. No information was available for one study. In BMP reports with more than 100 subjects, one or more authors received payment of more than $10 million. In the absence of standardized definitions and clearly specified ascertainment protocols, investigator judgments, such as achievement of successful arthrodesis or nonunion, the presence of ambiguously defined adverse events, or relatedness of a complication to the experimental device are susceptible to bias. Large payments or the prospect of future payments may have influenced investigator judgments in these open-label trials.

How do we not get fooled again?

Regulators, spine surgeons, hospitals, payers, and patients can help in avoiding folly in the future. The FDA can reinvigorate its mission of safety surveillance and public reporting. In PMA studies for spinal technology, the FDA can establish standard definitions for a few key complications, require consistent ascertainment across studies, and report them in simple formats for public documents, Web sites, and product labels. The short list of complications may begin with reoperation, readmission, infection, neurological deficit, life-threatening complication, and death. Surgeons and our professional associations would be well served by a little more skepticism for information from financially conflicted sources. Independent trials may yield quite different conclusions for BMP [21]. Consistent with Codman's vision for the End Result Idea [22], hospitals will better serve patients if they compare their complications for new procedures with FDA PMA data and share the findings with patients to enable better treatment decisions.

Acknowledgments

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Review Article

Bone morphogenetic protein-2 and spinal arthrodesis: the basic science perspective on protein interaction with the nervous system

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Abstract

The use and ''off-label'' indications for recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal arthrodesis have been significantly expanded over the last decade. New surgical approaches and pathologies treated often place the exogenous protein near the spinal cord or peripheral nerves, yet little data exist to the potential interaction between rhBMP-2 and the nervous system. The current review was undertaken to provide a basic science perspective on the wide-ranging effects that rhBMP-2, a potent growth factor, has on the injured spinal cord and the local dorsal root ganglia (DRG). Results from the early animal studies on neural safety of rhBMP-2 were compared with the more recent in vivo work characterizing protein impact on the injured spinal cord. Potential mechanism of the rhBMP-2–induced radiculitis after lumbar arthrodesis is also discussed.

The original pre-FDA approval animal study did not uncover any interaction between rhBMP-2 and the spinal cord or the nerve rootlets comprising the cauda equina. Recent in vivo work indicated, however, that in a penetrating injury model, rhBMP-2 triggers direct signaling in all spinal cord cells. In the rat, this interaction was deleterious to spontaneous recovery by exacerbating the inflammatory response to injury, increasing the glial scar, and making it more inhibitory to axonal regeneration. With respect to posterolateral lumbar arthrodesis in a noninjury model, rhBMP-2 use contributed to a transient postoperative mechanical hyperalgesia. Potential mechanism of this allodynia is through an observed inflammatory response within and around the local DRG.

In summary, contrary to the original beliefs in the clinical community, rhBMP-2 does elicit a profound signaling response within the spinal cord and the peripheral ganglia. Recent preclinical studies indicate that rhBMP-2, if provided direct access to the spinal cord parenchyma or the DRG, can trigger significant inflammation and morphologic changes within these tissues that could be deleterious to neurologic recovery. © 2011 Elsevier Inc. All rights reserved.

Keywords: Bone morphogenetic protein-2; Spinal arthrodesis; Basic science; Protein interaction; Nervous system; Spinal cord injury

Introduction

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has been used in clinical practice as an alternative to autologous bone grafting since its original Food and Drug Administration (FDA) approval in 2002 [1]. Despite the FDA approval of only a specific indication for its use in an anterior lumbar interbody fusion with a specific threaded cage, some surgeons have expanded rhBMP-2 indications to assist with obtaining spinal arthrodesis [2,3]. Specifically, a recent review of the Nationwide Inpatient Sample database by Ong et al. [4] indicated that in 2007 over 85% of all surgeries using the product were for apparently ''off-label'' applications. However, with the growing

volume of surgeries involving rhBMP-2, along with an increasing number of spine surgeons using the product in a variety of surgical approaches and spinal pathologies, additional complications have emerged. Among them are apparent neurological complications that were not reported during the early stages of rhBMP-2 development and clinical application [5–8]. Surprisingly, there are still limited basic science data concerning the direct effects of exogenous application of rhBMP-2 around the spinal cord and nerve roots.

Early work appeared to indicate little perceptible morbidity of rhBMP-2 on neurologic tissues. In 1999, Meyer et al. [9] performed a study in the dog model and reported on the safety of rhBMP-2 when used in a laminectomy defect in the lumbar spine. A critical review of the study reveals, however, that the authors only evaluated undecalcified plastic-embedded histological sections from the lumbar spine, that is, a histological examination of the roots or cauda equina using modern immunohistochemical (IHC) techniques was not reported. Furthermore, the authors applied a total of 0.24 mg of bone morphogenetic protein-2 (BMP-2), which would be equivalent to a human dose of 1.68 mg of rhBMP-2 (for a 70 kg patient based on the weight/dose ratio). This amount is significantly less than the clinical dosage used during spinal arthrodesis in adult patients undergoing lumbar surgery.

Meyer et al. acknowledged that BMP receptors are present in various central and peripheral nervous system cells. Use in the lumbar spine will more typically expose roots and cauda equina to rhBMP-2, as the spinal cord most often terminates at the midbody of the L1 vertebra in humans. The nerve rootlets comprising the cauda equina are technically part of the peripheral nervous system, leaving the effects on the spinal cord fully unknown.

At the time of publication, Meyer et al. concluded that although rhBMP-2 elicited some bone formation at the laminectomy site, it did not cause any clinically significant neurological sequelae for the animals. Since that report, the vast majority of preclinical studies have focused on the efficacy of rhBMP-2 in eliciting bone formation and enhancing fusion rates, whereas little work has been done characterizing its potential interaction with the spinal cord, nerves, or surrounding tissues [10–16].

Today, a number of postoperative complications including soft-tissue swelling, edema, heterotopic bone formation, and radiculitis have been described in the literature [17–20]. An increased rate of retrograde ejaculation was noted in the original FDA trial on rhBMP-2 use in anterior lumbar interbody fusion [21]. Similarly, FDA documents noted that back and leg pain adverse events were markedly higher in the early postoperative period after posterolateral fusion with both INFUSE and AMPLIFY (Medtronic Biologics, Inc., Memphis, TN, USA) formulations of rhBMP-2 [22].

As most trials of "off-label" use of rhBMP-2 have been for the treatment of degenerative spinal disorders, little is known about the potential hazards of using this product in other clinical circumstances. Spinal column trauma/fractures, similar to the FDA-approved use in open tibial fractures, could be a potential indication for rhBMP-2. Fractures and dislocations to the vertebral column are often associated with varying degrees of spinal cord, dural, or nerve root injury. Disruption in the mechanical barriers could expose the spinal cord parenchyma and other neurological tissues to the exogenous rhBMP-2 protein if placed in close proximity during surgical intervention. Similarly, in a non–trauma induced cervical myelopathy, there is always some degree of spinal cord damage, which may also affect barrier integrity, thus providing a potential access route for rhBMP-2 to the spinal cord if used in surgical management of this condition.

Driven by the paucity of basic science data on this subject, our group initiated a series of in vivo studies that aimed to ascertain the effects of rhBMP-2 on neural tissues when used during spinal arthrodesis after a spinal cord injury (SCI).

Spinal cord injury and acute response with rhBMP-2 exposure

In our initial study, we evaluated whether rhBMP-2 applied on an absorbable collagen sponge could diffuse within the spinal cord parenchyma and elicit a functional signaling cascade [23]. After a penetrating SCI, we performed a posterolateral arthrodesis, with or without rhBMP-2, at intervals ranging from 30 minutes to 21 days after injury. The extended time line allowed us to evaluate whether rhBMP-2 could enter the spinal cord and if so, whether this is dependent on the integrity of the blood spinal cord and meningeal barriers. Through immunohistochemical analysis, we explored whether there was BMP-specific signaling (phosphorylated Smad1/5/8 proteins) in neurons, astrocytes, oligodendrocytes, macrophages, and activated microglia, as well as in invading meningeal fibroblasts.

Overall, we observed a profound increase in the number of pSmad 1/5/8–positive cells within the spinal cord when rhBMP-2 was introduced to the spine at 30 minutes, 24 hours, or 7 days after an SCI. Bone morphogenetic protein–specific intracellular signaling activation confirmed our hypothesis that the protein can diffuse out of the carrier sponge, enter the spinal cord, and trigger functional changes in the central nervous system. In addition, we observed increased pSmad 1/5/8–positive staining in the inflammatory cells surrounding the lesion, which could lead to an exacerbated post-SCI inflammation. Interestingly, rhBMP-2 implantation to the spine at 21 days after SCI did not elicit an appreciable increase in pSmad 1/5/8 immunoreactivity within the spinal cord when compared with control rats. This time point correlated with restoration of the blood spinal cord barrier; therefore, we believe that significant intraparenchymal rhBMP-2 infiltration is directly dependent on the integrity of the protective barriers.

Our data showed that all endogenous spinal cord cells, as well as invading macrophages, are functionally

Carrier Control　　　　**rhBMP-2**
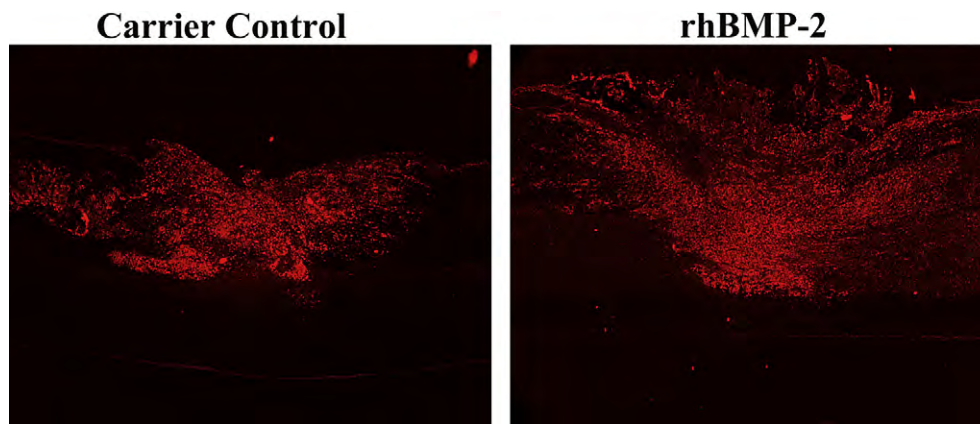
Fig. 1. Longitudinal sagittal sections through the lesioned spinal cord 7 days after SCI and arthrodesis. (Right) Increased macrophage and activated microglia response in the recombinant human bone morphogenetic protein-2–treated rats. Magnification 20×.

responsive to rhBMP-2. This initial project did not, however, provide insight into any morphologic or functional changes resulting from rhBMP-2 signaling after an SCI.

Spinal cord injury, morphologic changes, and functional recovery with rhBMP-2 exposure

We, therefore, performed a second investigation using the same rat model of penetrating SCI [24]. In this in vivo study, rats received either rhBMP-2 or saline on an absorbable collagen sponge 30 minutes after a spinal cord hemisection and were followed for 1 or 6 weeks postoperatively. The rats' functional recovery was tested, and spontaneous changes in fine and gross motor control were recorded. After sacrifice, spinal cord morphology was examined for the presence of the extracellular matrix proteins, specifically chondroitin sulfate proteoglycans, which are highly inhibitory to axonal regeneration [25]. We were also interested in whether an inflammatory response, previously documented in other soft tissues with rhBMP-2 exposure, would be exacerbated in the central nervous system tissues

examined in this model. In addition, we wanted to evaluate whether any observed changes appeared to affect functional recovery from the experimental SCI.

Postmortem analysis of rats sacrificed at 1 week after lesion indicated a number of morphologic changes in rhBMP-2–treated animals. Specifically, rhBMP-2 implantation triggered a profound inflammatory reaction within the spinal cord parenchyma as evidenced by increased ED-1 staining for activated microglia and invading macrophages (Fig. 1). Compared with the saline control group, ED-1 staining in spinal cords from rhBMP-2–treated animals was 81% greater. Additionally, glial fibrillary acidic protein staining for reactive astrocytes bordering the lesion was increased by 181%, and meningeal fibroblast labeling was 157% higher in these animals. Chondroitin sulfate proteoglycan staining revealed a twofold increase in protein immunoreactivity in the rhBMP-2–treated animals compared with saline controls. Increased astrocyte reactivity contributes to a larger glial scar forming within the spinal cord, which constitutes a physical and chemical barrier to axonal regeneration after injury (Fig. 2). The chemical composition of the scar, including the presence of chondroitin

Carrier Control　　　　**rhBMP-2**

Fig. 2. Glial fibrilary acidic protein staining of longitudinal sagittal sections through the lesioned spinal cord taken 7 days after SCI and arthrodesis. (Right) Recombinant human bone morphogenetic protein-2 treatment contributed to the increased astrogliosis around the lesion epicenter. Magnification 20×.

sulfate proteoglycans, adds to the nonpermissive nature of the scar and can further limit spontaneous recovery.

Proinflammatory effects of rhBMP-2 on the surrounding musculature have been recently reported [6,8,26]; however, our study was the first to document a similar response within the spinal cord [24]. In the central nervous system, the extent of postinjury inflammation has been directly correlated with the severity of persistent neurologic dysfunction [27]; therefore, the rhBMP-2–induced macrophage response observed in our study could serve as an impediment to neurologic recovery. In fact, at 1 week after lesion, we observed a pronounced worsening of functional recovery in rats treated with rhBMP-2 in both fine motor control and open-field ambulation.

Postmortem evaluation of the 6-week group revealed similar trends in morphologic differences between the spinal cords of rhBMP-2 and control-treated rats. These observed alterations appeared to result from a direct deleterious action of rhBMP-2 on the injured spinal cord after SCI and not secondary to mechanical compression of the spinal cord by the maturing fusion mass. This was demonstrated by controlling for mechanical compression with micro-computed tomography scanning, which revealed no evidence of bone encroaching into the spinal canal.

At 6 weeks after lesion, intraparenchymal inflammation remained elevated in the rhBMP-2–treated rats. Likewise, astrocyte immunoreactivity around the lesion core was more than 50% greater than in the untreated controls, and staining for an inhibitory extracellular matrix protein, NG2, was significantly elevated in the rhBMP-2 group. Functionally, we continued to see differences in the change of hind-paw angle of rotation, which is a measure of fine motor control disruption; however, gross locomotor activity was equivalent between the groups.

An unexpected finding observed in this study was the difference in postoperative onset of autophagia or self-mutilation between the rhBMP-2–treated and control rats. In the rat model of SCI, postinjury autophagia may indicate neuropathic pain [28]. In our study, 56% or rhBMP-2–treated rats, compared with 31% of control rats, required treatment for autophagia. Intraparenchymal inflammation and astrogliosis are associated with nociception [29,30]; however, additional research is needed to determine whether rhBMP-2 has a direct effect on inducing autophagia.

Future directions of research on rhBMP-2 effects on neurologic tissue

Currently our group is engaged in a further in vivo rat study aimed at evaluating the effects of posterolateral arthrodesis with rhBMP-2 in the lumbar spine on morphologic changes within the dorsal root ganglia (DRG) and spinal cord that could lead to the development of postoperative radiculitis (Table).

Our initial data indicate that rats treated with rhBMP-2 develop heightened mechanical hyperalgesia 3 days after surgery, which persists through day 7 but dissipates by the tenth postoperative day. On the cellular level, postmortem IHC assessment of DRG samples taken from animals treated for 7 days with rhBMP-2 showed increased macrophage staining (ED-1) (Fig. 3).

This finding coincides with the clinical reports on early postoperative radiculitis [31]. As our study was performed in the rat model, the time line of symptom resolution (10 days postoperatively) is most likely extended in a similar clinical scenario. The rate of peripheral axon regeneration, neurologic recovery, and the associated processes are faster in the rat; therefore, a 10-day course of postoperative allodynia observed in the rat may last for months in human patients [32]. In support of this assumption, the FDA clinical data showed the radiculitis effect to last around 3 months after surgery [33]. Despite the challenges in drawing direct conclusions as to a possible time course of the rhBMP-2–induced hypersensitivity or pain after spinal fusion in humans, our present study successfully replicated the observed phenomenon. This in turn will allow our group and others to further investigate these effects and devise strategies to avoid or manage the complication. Based on our preliminary data, the mechanism of this allodynia

Table
Summary of the basic science findings and possible clinical correlations

Animal procedure	Tissue evaluated	Observed histological effects with rhBMP-2	Observed behavioral effects with rhBMP-2	Clinical correlation
Penetrating SCI	Spinal cord	Increased inflammation, glial scar, and inhibitory extracellular matrix proteins	Decreased open-field ambulation and fine motor control at 1 wk Persistent fine motor deficits at 6 wk compared with SCI+carrier control	Possible impaired or delayed SCI recovery
Lumbar posterolateral arthrodesis	L4–L5 DRG/nerve root	Profound macrophage infiltration in and around DRG	Increased mechanical allodynia between 3 and 10 d postoperatively	Radiculitis after PLF/PLIF/ TLIF [31,33]

rhBMP-2, recombinant human bone morphogenetic protein-2; SCI, spinal cord injury; DRG, dorsal root ganglia; PLF, posterior lumbar fusion; PLIF, posterior lumbar interbody fusion; TLIF, transforaminal lumbar interbody fusion.

Carrier Control   **rhBMP-2**

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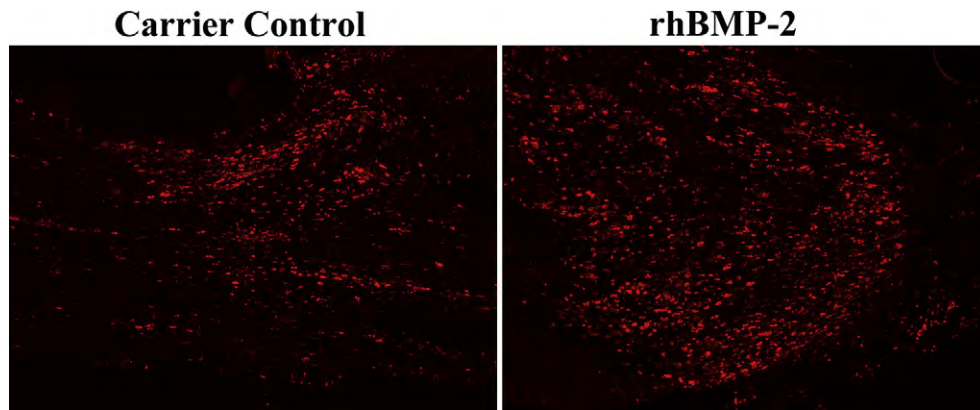
Fig. 3. Immunohistochemical staining of the L5 dorsal root ganglia (DRG) with ED-1. (Right) Upregulated macrophage activity is evident in rats undergoing L5–L6 spinal arthrodesis with rhBMP-2 compared with the DRG from the carrier control group (Left). Magnification 100×.

response is potentially through increased inflammation in and around the DRG.

Conclusion

These studies are the first to highlight some of the direct deleterious effects, at the cellular level, of exogenous high-dose rhBMP-2 on the central and peripheral nervous system. Although there is little doubt that rhBMP-2 and similar growth factors may promote bone induction, the relative benefits of rhBMP-2 fusion rates compared with potential and observed complications have not been well reported or analyzed, particularly in ''off-label'' indications. However, the range of negative or adverse effects with the use of this product has only recently become the subject of systematic research. Although our studies were performed in a rodent model, they raise some very important questions to the true impact of rhBMP-2 when applied around cells of the nervous system. And although rhBMP-2 has a well-established and proven role for certain specific indications, its dosage, delivery route, and carrier materials, and the mechanism of each contributing to observed complications, warrant significant further evaluation.

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Commentary

Commentary: Important considerations on bone morphogenetic protein-2 and neuroinflammation

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COMMENTARY ON: Dmitriev AE, Lehman RA Jr., Symes AJ. Bone morphogenetic protein-2 and spinal arthrodesis: the basic science perspective on protein interaction with the nervous system. Spine J 2011;11:500–5 (*in this issue*).

The growth factor recombinant human bone morphogenetic protein (rhBMP-2) came into very widespread clinical use before the very complex biologic activities of the molecule were well understood. Indeed, the complex biological actions of BMP-2 are still not completely established and remain under active study. As the Dmitriev et al. [1] review article describes, the interaction of BMP-2 with neurological tissue is an important issue.

At this point of time, the fact that BMP-2 induces inflammation is indisputable. We also know that along with this potent inflammatory process, BMP-2 stimulates the local formation of brown fat (with the production of heat and water via uncoupled mitochondrial activity) and ultimately leads to cartilage formation, neovascularization, and bone formation [2–4]. Very recent work has strongly suggested that there is a direct action of BMP-2 on peripheral nerves in a process that includes the direct induction of neuroinflammation. It further appears that this neuroinflammation may be basic to the process of BMP-2–induced bone formation [5]. This recent work, well summarized in the review by Salisbury et al. [5], demonstrates that the "release of BMP-2, such as during the induction of Heterotopic Ossification in soft tissue, initiates neurogenic inflammation within the local environment." This process appears to involve the participation of mast cells.

The frequent occurrence of new and "paradoxical" symptoms of leg pain, radiculitis, and sciatica in patients where BMP-2 had been applied near the spine may possibly be related to the direct interaction of BMP-2 with peripheral nerves or nerve roots within the surgical field. The Dmitriev et al. group also indicate that some of this effect may be because of direct effect on the dorsal root ganglia. Although these are currently early findings, the clinical complication involving apparent neurological effects (such as neuropathic pain, radiculitis, retrograde ejaculation, and so on) may be explained by these diverse mechanisms.

In the future, the clinical use of recombinant BMP-2 may need to be carefully considered with attention to the protection of nerve roots, their dorsal root ganglia, large nerves, and autonomic plexuses from the local area of rhBMP-2 application. For now, it is important to understand that the BMP-2 interaction with neurologic tissues is complex, involves a potent inflammatory response, and that the downstream effects are not yet well understood.

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Clinical Study

Adjacent vertebral body osteolysis with bone morphogenetic protein use in transforaminal lumbar interbody fusion

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Abstract

BACKGROUND CONTEXT: Recent studies have demonstrated cases of adjacent vertebral body osteolysis when assessing the effect of bone morphogenetic protein (BMP) on fusion rates. However, no study to date has evaluated the course of osteolysis at different periods.

PURPOSE: To determine the incidence and resolution of osteolysis associated with BMP used in transforaminal lumbar interbody fusions (TLIF).

STUDY DESIGN: Retrospective review.

PATIENT SAMPLE: All TLIF cases using BMP performed at one institution with routine postoperative computed tomography (CT) scans at defined intervals.

OUTCOME MEASURES: Area of osteolysis and fusion as determined by CT scan.

METHODS: We performed a retrospective analysis of all patients at our facility who underwent TLIF with BMP. Included were all patients who had obtained a CT scan within 48 hours of surgery, 3 to 6 months postoperatively, and 1 to 2 years postoperatively. Areas of osteolysis were defined as lucency within the vertebral body communicating with the interbody spacer that was not present on the immediately postoperative CT scan. Areas of osteolysis were measured in all three planes and the volume used for comparison of the 3 to 6 months CT scans with the greater than 1 year CT scan.

RESULTS: Twenty-three patients who underwent TLIF with BMP had obtained CT scans at all time periods required for evaluation. Seventy-eight vertebral bodies/end plates were assessed for osteolysis (39 levels). The incidence of osteolysis 3 to 6 months postoperatively in the adjacent vertebral bodies was 54% compared with 41% at 1 to 2 years. The mean volume of osteolysis was at 0.216 cm^3 at 1 to 2 years compared with 0.306 cm^3 at 3 to 6 months (p=.082). The area/rate of osteolysis did not appear to significantly affect the rate of fusion or final outcome with an overall union rate of 83%.

CONCLUSIONS: The rate of osteolysis decreased at 1 year compared with 3 to 6 months, but only 24% of the vertebral bodies with evidence of osteolysis at 3 to 6 months completely resolved by 1 year. Published by Elsevier Inc.

Keywords: Osteolysis; Resorption; Transforaminal lumbar interbody fusion; Bone morphogenetic protein

The disclosure key can be found on the Table of Contents and at www. TheSpineJournalOnline.com.

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EVIDENCE & METHODS

Context

Based on original industry-supported reports of positive outcomes with no unanticipated adverse events, PLIF/TLIF procedures have become the most common use of rhBMP-2 as a bone graft substitute. Complications associated with this product, however, are now being reported with concerning frequency. Establishing a clear risk-benefit assessment for rhBMP-2 use has been difficult, as the reporting of adverse events has been widely variable.

Contribution

In this retrospective study using computed tomography scans, the authors found that roughly half of the vertebral bodies in contact with BMP demonstrated osteolysis at 3 to 6 months after surgery, and that the osteolysis appeared to decrease (incidence and volume) at 1 year. Fusion rates at 1 to 2 years after surgery were 83%.

Implication

Osteolysis is an extremely common adverse event. The common persistence of boney defects up to 1 year after surgery is new information. Neither of these adverse event findings was reported in the original industry-sponsored study of this product. Very minor osteolysis may have little clinical impact, however very large defects as shown in this article may be very problematic if a revision surgery is required, if bone loss interferes with screw purchase, or if cavity formation predisposes or complicates deep wound infection. This study is underpowered to detect those associations. That rhBMP-2 may form bone in the interbody space is clear. That undesirable biological and clinical effects are frequent is equally clear. The value of rhBMP-2 in this setting of generally healthy patients, however, is undetermined.

—The Editors

Introduction

Transforaminal lumbar interbody fusion (TLIF) is a well-described method for obtaining interbody fusion from a posterior-only approach, and successful outcomes have been published from our facility and others [1,2]. Recently, the use of bone morphogenetic protein (BMP) has gained popularity and has been widely used inside interbody devices from an anterior approach after Food and Drug Administration approval for this indication [3–5]. Although initial studies reported a good safety profile of BMP when used in interbody fusions, recent literature has demonstrated an association between the use of BMP in interbody devices and the development of vertebral

body osteolysis [6–8]. It is important to note that use of recombinant human bone morphogenetic protein (rhBMP) in an interbody device using the TLIF approach is an off-label application of the product.

In a retrospective review of BMP use with TLIFs, McClellan et al. [6] reported resorption in 69% of patients in their series. To avoid this complication, Burkus et al. [9] advocated avoiding overstuffing the absorbable collagen sponge during the insertion of rhBMP-2 into the interbody device. Additionally, the use of BMP in a femoral ring allograft during an anterior lumbar interbody fusion has demonstrated resorption of the femoral ring allograft with nonunion rates approaching 56% compared with 36% in their iliac crest autologous control group [10]. Conversely, in a subsequent study, Slosar et al. [3] demonstrated that augmenting femoral ring allograft with BMP in an anterior lumbar interbody fusion procedure with posterior implants improved fusion rates to 100%.

Although a few case studies and reports have associated BMP use in TLIFs with osteolysis, to date no study has quantified the amount of osteolysis present at different times postoperatively or correlated the fusion rates of patients demonstrating osteolysis. The occurrence of osteolysis raises concerns about the application of BMP for use in TLIFs. This is the first study in the literature to evaluate the incidence and consolidation of osteolysis at various time points postoperatively and correlate this to fusion rates at final follow-up.

Materials and methods

After institutional review board approval, a retrospective review of all patients at our facility who underwent TLIF was performed to identify all patients who had rhBMP-2 (Infuse; Medtronic, Inc., Minneapolis, MN, USA) placed during their interbody fusion. Currently, the use of rhBMP-2 in the intervertebral disc space during a TLIF procedure is an off-label application of this product. The quantity of BMP was controlled in this study with 6 mg of rhBMP-2 being placed within the interbody space. Additionally, all cages were either Hydrosorb or Capstone (Medtronic, Inc., Minneapolis, MN, USA) and were placed unilaterally. At each level, one-fourth of a large BMP (3 mg) was placed into the interbody spacer with an additional 3 mg placed anterior to the interbody spacer on an absorbable collagen sponge. The remainder of the BMP was placed posterolateral with allograft opposite the side of the facetectomy. Further inclusion criteria mandated that all patients had obtained a computed tomography (CT) scan within 48 hours of surgery, 3 to 6 months postoperatively, and 1 to 2 years postoperatively. It is routine at our facility to obtain a CT scan in the perioperative period to verify implant position and postoperatively assess for fusion. Osteolysis was defined as a lucency within the vertebral body communicating with the interbody spacer that was not present on the immediate postoperative CT scan.

Fig. 1. Case example of a 48-year-old man who underwent an L5–S1 transforaminal lumbar interbody fusion with bone morphogenetic protein and subsequently developed postoperative osteolysis seen on the axial, sagittal, and coronal computed tomography scans performed at 5 months. Additionally, there is no evidence of bridging bone or interbody fusion at this time. At his most recent follow-up, there was evidence of posterolateral fusion, and he remains asymptomatic.

Furthermore, a well-defined border was necessary to identify an area of osteolysis. Areas of osteolysis were measured in all three planes (x, y, and z) on the axial, sagittal, and coronal reconstructions, with the area of osteolysis assumed to be cubic in appearance. The calculated volume was used for comparison of the 3 to 6 months CT scans with the CT scans obtained at greater than 1 year after surgery (Fig. 1). Fusion was determined by both flexion/extension radiographs and CT scans at final follow-up, but because we used BMP to obtain an interbody fusion, we only used the CT scan results for the purpose of this study. We used the presence or absence of bridging bone on CT scan to evaluate for interbody fusion and attempted to correlate this with osteolysis. For statistical analysis, we used a paired *t* test to compare the volumes of osteolysis, chi-square test to evaluate differences in fusion rate, and the kappa statistic to correlate osteolysis with fusion.

Results

Twenty-three patients who underwent TLIF with BMP had obtained CT scans at all three time periods required for evaluation. During the same period of this study, 88 patients underwent TLIF with BMP, but 65 patients (74%) were excluded as they did not have adequate postoperative imaging during the required time points. There were 5 women and 18 men with an average age of 38.2 years at the time of surgery (range, 23–81), demographics similar to those commonly treated at our facility. The 39 individual levels performed were divided as follows: 16 L5–S1, 16 L4–L5, 6 L3–L4, and 1 L2–L3. Twelve patients underwent a TLIF at only one level, whereas there were six two-level TLIFs, and five three-level TLIFs. Seventy-eight vertebral bodies/end plates were assessed for osteolysis (39 levels).

The incidence of osteolysis 3 to 6 months postoperatively in adjacent vertebral bodies was 54%. Comparatively, the incidence at 1 and 2 years was 41% (Fig. 2). Twenty-four percent of patients had resolution of their osteolysis from the short-term to intermediate-term follow-up period. Although

not statistically significant, the mean volume of osteolysis was less at 1 to 2 years compared with 3 to 6 months (0.216 cm^3 and 0.306 cm^3, respectively) (p=.082).

When evaluating for bridging bone on the CT scans, the interbody fusion rate was 83%. Computed tomography scans enabled us to focus on the interbody fusion, which was the purpose of placing the BMP. The area or rate of osteolysis did not appear to affect the rate of fusion as there was no difference in the fusion rate between the patients with evidence of osteolysis and those without (p>.05). Additionally, there was no correlation between the osteolysis and the presence of fusion.

Discussion

The use of BMP has increased dramatically in recent years after Food and Drug Administration approval for its placement inside interbody spacers for anterior lumbar interbody fusions. Reported advantages of the use of BMP as opposed to allograft or autograft alone include higher fusion rates, earlier time to fusion, and avoidance of the morbidity associated with iliac crest bone harvesting [3–5]. The advantages of the TLIF procedure, namely an increase in foraminal height, improved biomechanical properties, and, most notably, the ability to obtain a 360° circumferential fusion while avoiding the anterior approach, along with early reports of successful
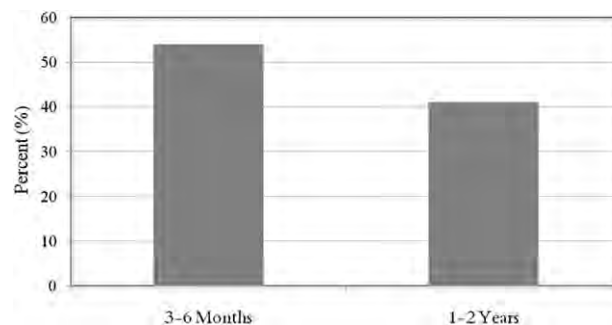

Fig. 2. Percent osteolysis from 3 to 6 months compared with 1 to 2 years.

fusion and low rate of complications lead to the "off-label" use of BMP as an adjunct to increase early fusion rates in TLIF procedures [1–5]. Initial reports of BMP use were promising; however, with increased use, reports of vertebral body osteolysis emerged [6–8].

At 3 to 6 months, the incidence of osteolysis was 54%, which dropped to 41% at 1 to 2 years. Although the incidence of osteolysis decreased during this time, 76% of cases of osteolysis failed to resolve. The mean volume of osteolysis was less at 1 to 2 years compared with 3 to 6 months, but this was not considered statistically significant (p=.082). The area, or rate, of osteolysis did not appear to significantly affect the rate of fusion or final outcome with an overall union rate of 83%, but most of these patients retained a bony void at ultimate fusion.

Although our study contains several weaknesses, the most compelling one is its retrospective nature. Being retrospective, it is subject to all the limitations and biases affecting every retrospective study. Unfortunately, we do not have a comparison group of patients (ie, autograft) as it became standard at our facility to use BMP with TLIFs. Although we admittedly do not have a control group, we feel this data need to be reported into the literature as very little evidence currently exists describing osteolysis. Furthermore, without a control group, no definitive conclusions can be drawn from this retrospective analysis.

Recently, studies aiming to assess the effect of BMP on fusion rates in interbody fusion procedures have demonstrated cases of adjacent vertebral body osteolysis [6,7]. A retrospective study conducted by McClellan et al. [6] demonstrated osteolytic defects in 69% of levels analyzed by CT scans 3 months postoperatively after TLIF with BMP. This study could not analyze the effect of osteolysis on fusion, as the follow-up was too short to allow for fusion to develop. More recently, Vaidya et al. [7] demonstrated graft subsidence at a rate of 53% with a mean of 24% graft height decrease after TLIF with BMP. Although they demonstrated 100% fusion with BMP, they had a fusion rate of 98% with allograft and demineralized bone matrix with significantly fewer cases of graft subsidence (12% occurrence rate with 12% graft subsidence) [7]. Last, Lewandrowski et al. [8] reported a series of five patients with osteolysis at the L5–S1 border after TLIF with BMP. All patients had presented with new onset severe postoperative back pain between 4 and 12 weeks. In their series, all pain resolved with conservative measures. In all of these studies, only those patients who had continued pain or other postoperative complications obtained CT images. No calculation of rate of formation or volume of osteolysis or effects on fusion rates was determined [6–8].

Overall, our rate of fusion with the TLIF procedure was similar to those reported in other studies (83%). We found a rate of osteolysis of 54% at short-term follow-up, which was also similar to the 53% reported by Vaidya et al. [7].

One benefit of conducting this study at our facility is the postoperative course by which we routinely obtain perioperative and postoperative CT scans on our patients to assess for proper implant placement and fusion, respectively. Because of this, we were able to evaluate the rate of formation and quantify the volume of osteolysis. However, as this study was retrospective, not every patient undergoing TLIF was included as they did not have CT scans obtained at all three time points. This is an inherent limitation of a retrospective review; however, we believe that our results demonstrate a potential limitation of the use of the BMP during this procedure. We have a unique patient population consisting of highly active young adults who tend to engage in strenuous activities. Our average patient age (38.2 years) is noticeably lower than those reported in other studies and may not be representative of the patient population at other facilities.

The use of BMP in TLIFs is associated with a high rate of osteolysis in the first 3 to 6 months. Although the incidence of osteolysis decreased at 1 year, most cases of osteolysis did not resolve and were present at ultimate fusion. The overall rate of fusion did not appear to be significantly affected by the osteolysis but indicates that surgeons should exercise caution when using BMP in interbody fusion procedures. More critical evaluation in clinical trials is needed to better understand the implications of the use of BMP with the TLIF procedure.

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Clinical Study

Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: a cohort controlled study

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Abstract

BACKGROUND CONTEXT: The commercially available growth factor recombinant bone morphogenic protein-2 (rhBMP-2) used in spinal fusion has been associated with numerous adverse reactions, including inflammatory reactions in soft tissue, heterotopic bone formation, radiculitis, osteolysis, and cage or graft subsidence. The original Food and Drug Administration Summary of anterior lumbar interbody fusion (ALIF) reported 12 retrograde ejaculation (RE) events (8%) in the rhBMP-2 groups compared with (1.4%) in the control group. It had been debated whether this finding was related to rhBMP-2 use.

PURPOSE: To compare the incidence of RE after ALIF in patients with and without rhBMP-2 use.

STUDY DESIGN: Retrospective analysis of prospectively gathered outcomes data on consecutive subjects having ALIF with and without rhBMP-2 use.

PATIENT SAMPLE: Male patients with lumbar spondylosis or spondylolisthesis having ALIF of the lowest one or two lumbar levels with and without rhBMP-2.

OUTCOME MEASURE: Report of RE as a new finding after ALIF.

METHODS: From the comprehensive outcome database at a high-volume university practice, male subjects having ALIF for one- (L5/S1) or two-level (L4/L5, L5/S1) lumbar fusion were identified. Retrograde ejaculation events were recorded and comparative incidence compared.

RESULTS: The two groups were comparable for age and additional procedures performed. There were 69 L5/S1 ALIFs performed with rhBMP-2 and 174 ALIFs performed without rhBMP-2 during the study period. Of those, 24 and 64 were two-level ALIFs performed with and without rhBMP-2, respectively. There were five RE events (7.2%) reported in the rhBMP-2 group and 1 (0.6%) in the control group. Comparing single-level L5/S1 ALIF, there was a 6.7% and 0% rate of RE in the rhBMP-2 versus control groups, respectively. At 1 year after surgery, three of six affected subjects reported resolution of the RE.

CONCLUSION: This study confirms previous reports of a higher rate of RE in ALIF procedures using rhBMP-2. This may be an important consideration in subjects concerned with sterility after surgery.   © 2011 Elsevier Inc. All rights reserved.

Keywords: Anterior lumbar interbody fusion; Retrograde ejaculation; Growth factor rhBMP-2

EVIDENCE & METHODS

Context
Retrograde ejaculation (RE) is a known complication of the anterior approach to the lumbar spine, particularly for interbody fusion at L5–S1. Previous reports have suggested that ALIF using rhBMP-2 might increase the risk of RE when compared to procedures in which BMP is not used. This study sought to confirm or contest these findings.

Contribution
In this retrospective case series report, the authors found that 7.2% of patients in whom BMP was used during ALIF had resultant RE, versus 0.6% in those in whom BMP was not used.

Implication
With the limitations of the study acknowledged, these data are similar to previous reports suggesting increased risk of RE with use of BMP during ALIF at L5–S1. These findings are likely to be important when discussing the risks and complications of this type of surgery with patients.

—*The Editors*

Introduction

Anterior lumbar interbody fusion (ALIF) may be complicated by retrograde ejaculation (RE) in male patients. The autonomic plexus coordinating bladder sphincter control during ejaculation is intimately associated with the aortic and vena cava and drapes down over the bifurcation and ventral surface of disc and sacral body. This area is necessarily manipulated during an approach to the lower lumbar segments, particularly L5/S1. The reported rates of RE have varied and can be associated with the magnitude of the dissection, the number of levels exposed, and possible soft-tissue debridement necessary in revision, infection, or tumor surgery [1–4].

The commercial human recombinant bone morphogenic protein-2 product (rhBMP-2), INFUSE (Medtronic Inc., Memphis, TN, USA), has been approved for use in the lumbar spine in association with ALIF with an LT-cage (Medtronic Inc.) [5]. The LT-cage is a threaded wedge-shaped cage that engages and distracts the disc space on application. Since its introduction, rhBMP-2 has been associated with multiple serious adverse effects, including soft-tissue swelling, local inflammation, sterile cyst formation, osteolysis, and implant migration, as well as possible increased risk of malignancy in the high-dose AMPLIFY formulation (Medtronic Inc.) [6–22].

The original publications of rhBMP-2 with the LT-cage for ALIF reported no adverse events associated with rhBMP-2. Food and Drug Administration (FDA) documents [23] reported more RE events in the rhBMP-2 group as compared with a control receiving iliac crest bone graft (ICBG) and no rhBMP-2. Smoljanovic et al. [17,24,25] have suggested this effect may be because of either ectopic bone formation in the area ventral to the disc or an inflammatory reaction associated with rhBMP-2. Burkus et al. have denied any association of the RE events with rhBMP-2 [17].

The senior surgeon began using rhBMP-2 in 2003 as a substitute for or augmentation to other fusion techniques for ALIF. We had collected a prospective database on all surgical cases, complications, and outcomes before and after this period of rhBMP-2 introduction. Some of these data have been previously published [26–28]. To investigate the possible effects of rhBMP-2 on the rate of RE after ALIF, we have retrospectively analyzed the data from three years, 2002 to 2004. During this time we began to use rhBMP-2. In this study, we compared the rate of RE in patients who did and did not receive the rhBMP-2.

Methods

Study design and patient selection

Patients of the senior author (EJC) who underwent surgery on investigational protocols for disc herniation, spondylosis, and spondylolisthesis were prospectively enrolled, and preoperative clinical data, operative details, postoperative complications, and postoperative outcomes were recorded by independent research assistants in a deidentified database. Details of the enrollment and data collection protocols have been previously published [26–28]. Specific data collection on RE was included for follow-up of all subjects undergoing anterior lumbar surgery.

From this database during the years 2002 to 2004, patients having one- or two-level ALIF for degenerative spondylolisthesis, low-grade isthmic spondylolisthesis, recurrent lumbar disc herniation, or presumed discogenic pain were identified. Patients were included if the lumbar fusion crossed one- or two-disc levels and included the L5/S1 level. The L5/S1 level was operationally defined for this study as the lowest mobile segment of the lumbar spine with its disc below the aortic bifurcation. That is, regardless of the number of anatomic lumbar vertebrae, the lowest mobile disc below the bifurcation (which determined the dissection) was considered L5/S1.

The 2002 to 2004 time period was selected to include a mix of cases before and after rhBMP-2 was introduced while the surgical indications and technique would have been relatively constant. In 2005, the senior author (EJC) temporarily left his usual university practice for active duty with the US military, and this provided a natural time break for this analysis.

From the data set, a retrospective analysis of the prospectively gathered outcomes data on consecutive subjects

having ALIF with and without rhBMP-2 use was performed regarding the complication of RE.

Purpose

To compare the incidence of RE after ALIF in patients with common lumbar pathology undergoing an ALIF, which included L5/S1 with and without rhBMP-2 use.

Hypothesis

Patients undergoing one-or two-level ALIF including L5/S1 via an open retroperitoneal approach would report RE at the same rate whether rhBMP-2 had been used in the ALIF or not.

Surgical technique

The senior author (EJC) did all the surgical approaches. He had extensive experience with the anterior and anterior-lateral approaches to the spine and trained at the University of Hong Kong and Duchess of Kent Children's Hospital specifically in this technique (1989). At the start of this study, he had 12 years experience doing his own anterior surgical approaches to the spine (1,000 cases or more).

The lower lumbar spine was exposed using a retroperitoneal approach. Depending on the patient's weight and abdominal obesity, either a medial transrectus approach (if thin) or less commonly an anterior-lateral muscle–splitting approach was used. Blunt dissection to the lower one or two discs was performed, and the iliolumbar vessels ligated and transected when necessary to approach L4/L5. No electrocautery was used in male patients at the level of bifurcation of the deep vessels or around the L5/S1 disc. At L5/S1, the middle sacral vessels were ligated and transected or sometimes swept bluntly to the side. The delicate autonomic plexus was divided with a sharp vertical incision in the midline from the bifurcation of the aorta caudally and retracted to either side using a dental roll blunt dissector. If the plexus appeared densely adherent to the disc or bone, several cubic centimeters of sterile saline was injected just ventral to the anterior longitudinal ligament with a long 25-gauge needle to create a dissectible plane in which mobilizes the plexus.

Once the exposure was achieved, it was maintained with a self-retaining retractor. The disc edges were incised off bone with a long scalpel, and the disc was removed piecemeal. End plates were perforated in their center with punctures from a small curette, and a femoral ring allograft (FRA) or titanium mesh cage was placed with the disc space under tension. If rhBMP-2 was not used, local osteophytes or ICBG were used as autograft often along with demineralized bone matrix grafting material. If rhBMP-2 was used, two sponges (Small Kit, 4.2 mg rhBMP-2; Medtronic Sofamor Danek, Memphis TN) were placed inside the FRA central canal. Unless a four-hole plate was used in a stand-alone configuration, a buttress screw was placed, usually, into the caudal vertebrae just below the end plate.

Posterior instrumentation, either unilateral or bilateral, was placed as deemed necessary by the pathologic instability of the segment or bone quality.

Statistical analysis

Fisher exact test was used to compare binomial data in which low-frequency events (eg, RE) were anticipated. Statistical significance for complications was determined according to the severity of event, and the potentially serious or catastrophic events (eg, sterility, neurologic injury) were considered significant at a p value of less than 0.2. Number needed to harm (NNH) was computed to determine the number of patients treated with rhBMP-2 to produce one patient suffering harm due to a specific rhBMP-2–associated adverse-event treated (eg, if the risk of a certain adverse event in the treatment group is 10% vs. 0% in the control group, the NNH is 10).

Results

There were 174 patients identified as receiving an ALIF without rhBMP-2 and 69 receiving an ALIF with rhBMP-2 by the inclusion criteria. The groups were well matched for age, diagnoses, and number of levels fused (Table 1). Most surgeries were performed using a direct anterior approach

Table 1
Demographic and clinical data

	rhBMP-2	Control
n	69	174
Age (SD, range)	42.4 (10.3, 22–65)	40.9 (9.9, 25–65)
Smoker (%)	18 (28)	42 (24)
Weight, kg (SD)	81 (12.1)	79 (13.4)
Diagnoses %		
Degenerative spondy	48	46
Recurrent herniation/DDD	19	23
Isthmic spondy	33	31
One-level ALIF (%)	45 (65)	110 (59)
FRA	68	172
Mesh cage	1	2
Local autograft	6	15
ICBG	0	3
Demineralized bone matrix	0	138
Transrectus retroperitoneal approach (%)	59 (86)	150 (86)
Anterior-lateral retroperitoneal approach (%)	10 (14)	24 (14)

Spondy, spondylolisthesis; DDD, low back pain illness presumed from degenerative disc disease; ALIF, anterior lumbar interbody fusion; ICBG, iliac crest bone graft; FRA, femoral ring allograft.

(medial transrectus), and virtually all received an FRA structural allograft. Only three mesh cages were used.

There were 45 single-level L5/S1 ALIFs performed with rhBMP-2 and 110 performed without rhBMP-2 during the study period; there were 24 and 64 two-level ALIF's performed respectively.

There were six RE events noted. All occurred after ALIF with FRA spacers, which were overwhelmingly most common spacer used. There was no association with diagnosis (p>.2): in the rhBMP-2 group, two had isthmic spondylolisthesis, two had degenerative spondylolisthesis, and one had presumed discogenic pain.

There were five RE events (7.2%) reported in the rhBMP-2 group and one (0.6%) in the control group (p=.0025). Comparing single-level L5/S1 ALIF, there was an RE rate of 6.7% and 0% in the rhBMP-2 versus control groups, respectively (p=.0233). There were relatively few patients having a two-level ALIF including L5/S1, and there were two RE events in the rhBMP-2 group and one in the control (p=.179) (Table 2).

Of the five patients having an RE event in the rhBMP-2 group, three had some apparent early osteolysis appreciable by plain radiograph in the early postoperative period. One patient had an extensive osteolysis with a fracture of the anterior half of the sacral body. This healed in time without gross displacement (there had been supplemental fixation at the first surgery). The RE was appreciated before the fracture was apparent on radiographs.

At 1 year after surgery, three of six affected subjects reported resolution of the RE: two in the rhBMP-2 group and one in the control group. The two oldest subjects reporting RE, aged 48 and 53 years, did not recover.

During the same study period, one patient having an L4/5 ALIF alone (ie, not included in this analysis but previously reported by this group) for isthmic spondylolisthesis may also have had RE [29]. This patient was diabetic with preexisting neuropathy and erectile dysfunction before surgery. It was difficult to be sure the complaint was in fact RE because of other neuropathic issues. At 6 months after surgery, this patient reported his sexual function had returned to his preoperative status. This was the only possible RE event in an ALIF patient having a lumbar level fusion excluded from this study. He had not received rhBMP-2.

Discussion

Anterior fusion with restoration of disc space height and lordosis may preserve better sagittal alignment and perhaps be associated with a more rapid recovery compared with posterolateral fusion techniques [29]. However, both anterior approaches and posterior lumbar interbody fusion approaches have risk of injury to intervening structures. Retrograde ejaculation is an uncommon complication of anterior fusion of the lower lumbar spine. The mechanism of the injury as a complication of anterior spinal surgery is thought to be a disruption of the superior hypogastric plexus in the retroperitoneal space around the level of the bifurcation of the aorta and the lumbosacral junction [30].

Estimates of incidence of RE after anterior lumbar surgery vary widely [3]. Kaiser et al. [1] reported a 45% incidence of RE after laparoscopic approach to the lumbar spine. At the other extreme, Kang et al. [4] report no RE after 412 minilaparotomic approaches to the lumbosacral spine. It is likely that both the true incidence and detection of RE after spinal surgery may vary by approach, technical expertise, concomitant pathology, and the intensity of the surveillance method.

The use of rhBMP-2 has been associated with various early inflammatory reactions, including soft-tissue swelling and sterile cyst formation. In the neck, these may result in life-threatening complications. In bone, rhBMP-2 may cause early osteolysis and can be associated with implant dislodgment, subsidence, and loss of alignment [6–22]. Obviously any of these events can theoretically affect the autonomic plexus.

Food and Drug Administration documents [23] and Smoljanovic et al. [17,24,25] also reported a high rate of RE associated with rhBMP-2 use in the LT-cage/rhBMP-2 trial (7.9%, rhBMP-2 group vs. 1.4%, ICBG group), overall (NNH=15, Fisher exact p=.05). With the laparoscopic approach, more than 9% of the patients in the FDA trial receiving rhBMP-2 and an LT-cage reported RE. In the randomized controlled trial phase of the FDA trial, there was an incidence of RE in 6.4% of male patients having an open ALIF with rhBMP-2 compared with 1.5% in the control (ICBG) group (NNH 20; Fisher exact p=.14).

Reporting on anterior interbody fusion in the setting of rhBMP-2 use, Jarrett et al. [2], in 2009, reported a 6.2%

Table 2
Retrograde ejaculation events

	rhBMP-2	Control	p Value*
L5/S1 (single level)	3 of 45 (6.7%, 90% CI: 0.55, 12.79)	0 of 110 (0%, 90% CI: <2.4)	.0233
L4/L5 and L5/S1	2 of 24 (8.3%, 90% CI: −0.95, 17.61)	1 of 64 (1.6%, 90% CI: −0.99, 4.11)	.179
Total	5 of 69 (7.3%, 90% CI: 2.11, 12.39)	1 of 174 (0.6%, 90% CI: −0.37, 1.51)	.0025

CI, confidence interval.
* Fisher exact test.
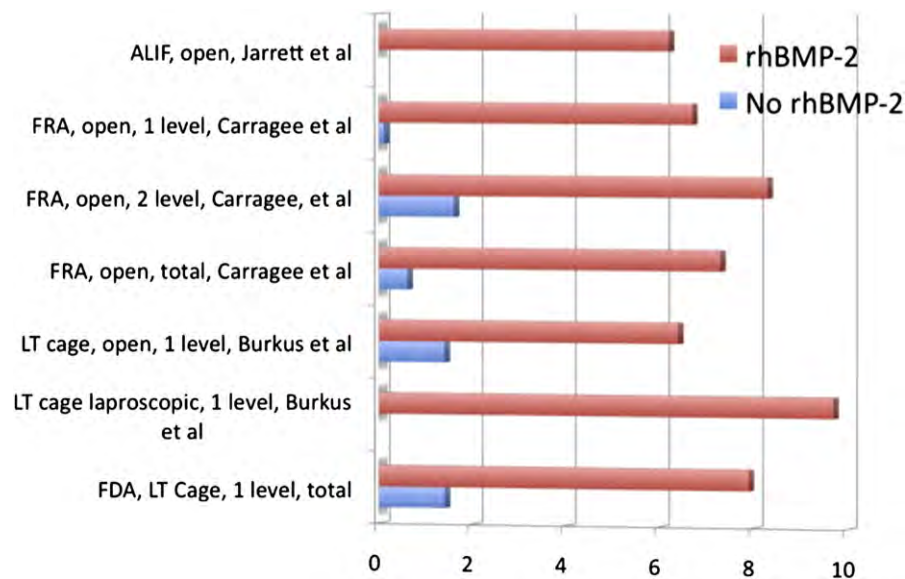
Figure. Comparison of retrograde ejaculation rates in male patients after anterior lumbar interobdy fusion (ALIF) from three studies: ALIF with recombinant bone morphogenic protein 2 (rhBMP-2) by Jarrett; femoral ring allographft (FRA)/rhBMP-2 vs. control group (single level and two levels) by Carragee et al.; LT cage/rhBMP-2 vs. control (open) group, LT cage/rhBMP-2 (laparaoscopic) group by Burkus et al.; and FDA data LT cage vs. control, total cases [2,5,17,23,24].

rate of RE. This is nearly identical to the rate reported by the FDA and Burkus et al. (6.4%). The rate in our review for patients receiving rhBMP-2 at a single level was also 6.7%. Our rate of RE in ALIF patients without rhBMP-2 was 0% and 1.6% for one- and two-level ALIF, respectively. Again this was very similar to the non-rhBMP-2 group in the FDA trial of FDA study (1.4%), but both were higher than reported by Kang et al. [4] (Figure).

The present study design has several inherent limitations and potential biases. The case review and analysis were retrospective with a database that did not allow primary chart review (perhaps biasing to lower rates of RE recognized). However, the surveillance for RE was the same for both rhBMP-2 cases and controls at the time of data collection and entry. Second, because a bilateral injury to the superior hypogastric plexus is more likely when dissecting between the bifurcation of the aorta [30], RE may be more common with ALIF involving the L5/S1 disc compared with a unilateral approach to L3/L4 or L4/L5. In our study design, all cases included an L5/S1 ALIF by case definition. It is likely, therefore, that the selection of ALIF cases that all involved at least the lumbosacral junction increased the incidence compared with a series that included fusion at higher levels without dissection to the lumbosacral junction. Finally, the placement of an FRA spacer may be less invasive, requiring less dissection than the placement of two threaded cages. Still, the reporting of RE rates from three separate series of 6% to 7% is much higher than both the FDA data (1.4%), the large series by Kang et al. (0%) and our previous and continuing experience of the senior author for ALIF without rhBMP-2 (0.5–1.5%).

Although uncommon, the risk of RE is an important potential complication for many male patients and their families. In a study at our institution of ALIF for isthmic spondylolisthesis, 8% of men refused anterior surgery because of the risk of RE, when the risk of RE was explained to them to be 1% or less (our previous experience) [29]. With the serious possibility that RE is associated with rhBMP-2 use in the lower lumbar spine, it is important that men be counseled about this risk and advised that avoiding rhBMP-2 in favor of alternative grafting methods may minimize the risk.

It is our practice to limit the use of rhBMP-2 with ALIF surgery to patients in whom the benefit is much clearer than appears to exist in the healthy patients undergoing single-level fusion in the rhBMP-2 industry-sponsored trials. Patients with a metabolic bone disease (eg, osteomalacia or osteoporosis), adverse exposure (eg, tobacco, radiation), or specific anatomic risks for nonunion may have a benefit to risk ratio favoring rhBMP-2 use. However, appropriate and specific discussion in male patients regarding the increased risks of sterility may be appropriate.

Conclusion

This study supports multiple lines of evidence that strongly suggest rhBMP-2 use with an anterior interbody fusion at the lumbosacral junction is associated with an increased risk of RE.

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Commentary

Commentary: Another complication associated with rhBMP-2?

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COMMENTARY ON: Carragee EJ, Mitsunaga KA, Hurwitz EL, Scuderi GJ. Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: a cohort controlled study. Spine J 2011;11:511–6 (*in this issue*).

Carragee et al. [1], in their article "Retrograde ejaculation after lumbar anterior interbody fusion using rhBMP-2: A cohort controlled study," bring into question yet another possible unanticipated complication that surgeons must consider when using a potent biological growth factor such as recombinant human bone morphogenetic protein-2 (rhBMP-2). The use of rhBMP-2 after its initial Food and Drug Administration (FDA) approval has escalated among North American spine surgeons. It was originally approved only for single-level anterior lumbar interbody fusions (ALIFs) using a titanium metallic cage device. However, once available, surgeons began to use BMP-2 in various "off-label" applications, such as posterolateral lumbar fusions [2], posterior lumbar interbody fusions [3], and anterior cervical fusions [4]. Although clinical efficacy in these applications has been shown to equal that of iliac crest bone grafting (presumably the "gold standard"), surgeons also began to report various complications with the use of rhBMP-2, which have been troubling. There have been established reports of early inflammatory reactions of soft-tissue swelling and sterile cyst formation. In the cervical spine, it has resulted in potentially life-threatening airway complications. In bone, rhBMP-2 has been associated with early osteolysis that has led to implant subsidence and loss of alignment [5–16]. In their study, Carragee et al. [1] add to this potential list of complications by reporting on a significantly higher incidence of retrograde ejaculation (RE) in male patients undergoing ALIF surgery with

rhBMP-2 when compared with those who did not have their fusions done with rhBMP-2.

The popularity of rhBMP-2 with spine surgeons seems to be based on the morbidity of taking autologous iliac crest bone graft (ICBG) and surgeon convenience. The proponents of using BMPs or other bone graft substitutes point to the major morbidity associated with iliac crest bone-graft harvest, citing risks of wound infections, hematomas, neuromas, and chronic hip pain. However, it is of interest that in every prospective randomized clinical study comparing BMP-2 with that of ICBG harvest, the overall patient-based outcomes never show a statistical difference between the two groups as measured with the use of the Oswestry Disability Index or the Short Form-36 [17,18]. If harvesting ICBG causes such painful morbidity that severely affects patients' lives, the outcome measures should support this premise. Therefore, one must wonder whether the pain associated with the bone graft site is really a significant major adverse factor at all. There is no question that opening a box of rhBMP-2 is very convenient and technically "easy" to do compared with harvesting the ICBG. This phenomenon may actually be the main reason why surgeons choose to use this product, because clinical outcome measures do not clearly demonstrate a statistically significant benefit. Everyday, we surgeons consider using a more expensive pedicle screw system if it seems "easier" to use, when we know fully well that the "new technology" will have little bearing on the outcomes. This phenomenon, which may be a strong driver of surgeon's behavior, has not been adequately studied in the literature.

The amount of health care dollars that is spent on spine care has escalated over the years, and it has now surpassed the dollars spent on hip and knee implants. To get a handle on health care spending in the United States, the federal government has targeted the spine as a major component in its attempt to reduce cost and eliminate wasteful

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spending from all tiers of spine care. Although this is a complicated topic with many different factors at play, there is no question that the introduction of rhBMP-2 has added a significant overall cost and is now a major contributor ($4,500 per kit) of the increased dollars spent on spine care. On the contrary, Carreon et al. [19] did a cost analysis of BMP-2 and concluded that BMP-2 is cost-effective when compared with the costs of revising the greater number of nonunions and complications that are associated with iliac crest bone grafting. If true, the net effect of such a conclusion should result in an overall dollar savings for spine care, and perhaps fewer overall operative procedures because of fewer complications. However, Martin et al. [20] showed that, despite technological advancements in spinal surgery in the 1990s, the overall cost of spine care in the United States and the total number of revision spinal operations being done have increased substantially over the ensuing decade. It is also quite possible that the number of fusion surgeries has increased because of the relative "ease" of doing a fusion operation with rhBMP-2. It seems that if spine surgeons are going to be using more expensive technology and drive up the cost of spine care, it would be prudent to definitively prove that we are getting "superior" results with our patients and that the new technology is truly "cost-effective."

In their article, Carragee et al. [1] point out another major complication that may be associated with rhBMP-2. They compared the incidence of RE in male patients undergoing one- and two-level ALIF surgery with or without rhBMP-2. This was a retrospective cohort analysis from a single academic surgeon who has vast experience in anterior lumbar surgery, and more importantly, from a surgeon who does not have any corporate conflicts of interest. They observed that the patients who had fusions with rhBMP-2 had a 7.2% incidence of RE compared with 0.6% in control patients. They confirmed previous reports of a significantly higher rate of RE in ALIF surgery when using rhBMP-2, and advised caution in patients who are concerned with sterility after surgery. Although basic scientists know a great deal about the effects of BMPs on bone, there is much that they do not yet understand on its effects on other tissues, especially with the large pharmacologic doses used for bone fusions. As a strong morphogenetic cytokine, BMP may have a potent effect on other soft tissues surrounding the spine and can therefore possibly explain the various complications that have been observed after its release into the market [7–9,12,13]. It would, therefore, seem very plausible that rhBMP-2 does indeed have a major effect on the autonomic plexus of the anterior lumbar spine. As pointed out by Carragee, it is of interest that the original publications of rhBMP-2 with lumbar tapered cages reported to the FDA did not cite any adverse events in spite of the RE rate of 6.4% in the rhBMP-2 group compared with 1.5% in the ICBG group [11,21]. Although the rates of RE seem similar in these studies, the authors seem to draw conflicting conclusions. There does not seem to be

any rational explanation for these observational differences other than the fact that Carragee et al. had no commercial conflicts of interest, whereas the original FDA studies were corporate-sponsored studies.

In this era of public scrutiny over surgeon's conflicts of interest, it would seem prudent to carefully assess studies that may strongly influence how surgeons practice their art. Although corporate-sponsored research is absolutely needed to help advance innovation and patient care, we must come to the hard realization that the data analysis and interpretation in such studies can be biased in favor of the funding sources. After all, it is against our nature to publish a negative result or an adverse event that condemns a product that is being studied if we are being funded by the sponsors of the product [22]. Therefore, it is of critical importance that independent studies (such as by Carragee et al.) be published so that the practicing surgeon gets a balanced view of the "truth."

In conclusion, we practicing surgeons have many issues to contemplate before we embrace a new technology as a new "gold standard." In the case of rhBMP-2, we must first determine whether there is good line of evidence that it truly provides a higher fusion rate and better clinical outcomes. Second, we must carefully study the potential adverse effects and complications that are associated with rhBMP-2 and weigh its advantages over such complications. Because the published reports may provide conflicting conclusions, we must also be sophisticated enough to realize that some of the data that is published on these topics do indeed have potential bias with conflicts of interest. Finally, we must be conscious of the escalating costs of spine care as it relates to the overall economic impact it is having in our society. There seems to be no doubt that rhBMP-2 has spared many patients of the "dreaded" ICBG harvest, but there is also no convincing data that demonstrates that it has significantly improved patient-based outcome measures. Carragee et al. [1] has now provided further evidence that rhBMP-2 is associated with increased rates of RE, thereby adding to the growing list of potential complications being reported as a direct consequence for using rhBMP-2. There does appear to be unique complications associated with rhBMP-2 that clinicians never saw with ICBG harvest. Therefore, whether the complications associated with rhBMP-2 is more clinically problematic versus those associated with ICBG harvest is up for debate and further study. As usual, we clinicians must weigh the risks and benefits to any procedure and use new technologies based on sound clinical judgment that provides the best cost-effective clinical outcomes for our patients.

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Commentary

Commentary: An evolving perception of the risk of rhBMP-2 use for anterior spinal interbody fusions

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COMMENTARY ON: Carragee EJ, Mitsunaga KA, Hurwitz EL, Scuderi GJ. Retrograde ejaculation after anterior lumbar interbody fusion using rhBMP-2: a cohort controlled study. Spine J 2011;11:511–6 (*in this issue*).

We are orthopedic surgeons who, working in Croatia, have been described as coming from different "ethnic, demographic, and training" backgrounds [1]. As such, perhaps we have had a unique approach to the critical analysis of reports related to the clinical use of recombinant human bone morphogenetic protein-2 (rhBMP-2; INFUSE Bone Graft; Medtronic Sofamor Danek, Memphis, TN, USA) for lumbar interbody fusion. Although there remain many unanswered questions, the issue of retrograde ejaculation (RE) has been clarified by the present study by Carragee et al. [2]. This retrospective comparative cohort study found a higher rate of RE after open, one- or two-level, anterior lumbar interbody fusion (ALIF), including L5–S1 using rhBMP-2 (7.2%; 95% confidence interval: 2.1, 12.4) compared with a rate of 0.6% (95% confidence interval: −0.4, 1.5) in non-rhBMP-2 controls. These rates are similar to those recently reported by Burkus et al. [3] for a combined observational and randomized clinical trial of single-level ALIF, with an RE rate of 7.9% in the rhBMP-2 group compared with 1.5 in the controls. However, the history of how this serious complication apparently associated with rhBMP-2 was neglected for many years deserves a careful review.

Our concerns began, in 2002, with the study by Burkus et al. [4], a multicenter, prospective, randomized, non-blinded, US Food and Drug Administration (FDA)-approved study. In this study, 279 patients with degenerative lumbar disc disease underwent ALIF using two tapered threaded

fusion cages (LT-CAGE; Medtronic Sofamor Danek). The investigational group (143 patients) received rhBMP-2 on an absorbable collagen sponge, and a control group (136 patients) received autogenous iliac crest bone graft. The results of the investigational group were reported to be better in comparison to the results of control group in some clinical and radiographic outcome measurements. The authors reported that "there were no unanticipated device-related adverse events in either treatment group." In time, the INFUSE Bone Graft was approved by the FDA based, in part, on authors' reported results of this study [5].

However, the reporting of results in this publication was irregular. Although results were generally compared item for item between the rhBMP-2 groups and controls, there were two outcome measurements that were not: adverse events related to harvesting of the iliac crest graft and RE. Although the first one is logical as no bone graft was harvested from the rhBMP-2 patients, the lack of documented comparison of RE between the control and rhBMP-2 others drew our attention. Apparently, six male patients (4.1%, of 146 male subjects) complained of RE after surgery [4].

Burkus et al. [4] did not report how many patients reporting RE were in the investigational arm and how many were in the control arm. The authors instead emphasized that the complication occurred in 13.3% (4 of 30) of the men who underwent a transperitoneal approach and occurred in only 1.8% (2 of 116) of men who underwent a retroperitoneal approach. That difference was statistically significant according to Fisher exact test (p=.017). However, it was confusing to us that in a randomized controlled trial (RCT) there was no mention of how many of the patients with this serious complication were from the investigational group compared with the control group.

Similar patient data were presented by Sasso et al. [6] 1 year later, in 2003. However, again there was no breakdown of the

rates of RE in rhBMP-2 patients and those without. It was instead concluded by the authors that the transperitoneal approach to the lumbar spine at L4–L5 and L5–S1 has a 10 times greater chance of causing RE in men than a retroperitoneal approach. That conclusion was challenged by Birch and Shaw [7], who found it to be at odds with their clinical experience. Birch and Shaw stated that either their patients have been extraordinarily lucky over the time or that there were confounding factors in the Sasso et al. study that might have contributed to the high rate of RE. Birch and Shaw did not discuss the confounding factor of rhBMP-2 (as the information was not provided by Burkus et al. [4] or Sasso et al. [6]), but such a comment by highly experienced spinal surgeons was an indication that further clarification of the issue was required. Sasso et al. did not respond to Birch and Shaw's letter [7].

One may ask how rhBMP-2 can be associated with RE, an uncommon complication resulting from an inability of the internal vesical sphincter, a muscle at the base of the bladder, to contract during ejaculation. It has been suggested by in vitro studies that rhBMP-2 exposure involves a notable host inflammatory response preceding the bone induction cascade [8,9]. This effect has been associated with the release of cytokines causing a local inflammatory response. Muchow et al. [10] histopathologically demonstrated this inflammatory process associated with rhBMP-2 use in spinal fusion. An increased incidence of postoperative radiculitis has been reported with the off-label use of rhBMP-2 during transforaminal interbody fusion [11,12]. Most of these patients had no identifiable structural cause of postoperative radiculitis. Furthermore, the rate of postoperative radiculitis appeared to be significantly reduced (from 20.4% to 5.4%) when the annulotomy site was sealed to protect the exposed nerve root and dura from the rhBMP-2 placed within the intervertebral space [12].

During the ALIF procedure described in the study by Burkus et al. [4], there was no barrier used to protect superior hypogastric plexus from rhBMP-2 exposure. This sympathetic plexus crosses the lumbosacral junction in retroperitoneal space immediately ventral to the interbody cages containing rhBMP-2. Damage or inflammation of the plexus at this point may result in RE.

In 2010, Burkus et al. responded to a letter from us in the *Journal of Bone and Joint Surgery* regarding RE rates [3,13,14]. In this letter, they indicated that 6.4% of the rhBMP-2-exposed male patients in the RCT developed RE compared with 1.5% of the control group. However, despite reporting the higher rate of RE in the rhBMP-2 group, the authors nonetheless categorically denied any relationship between the rhBMP-2 use and the onset of RE [3,13,14]. In our opinion, this categorical denial was not credible.

Over time, there has been a cumulative reporting of multiple independent authors regarding adverse effects of rhBMP-2. The present study by Carragee et al. [2] adds further data to this growing field, and we are hoping that remaining issues related to the adverse effects of rhBMP-2 use for spinal interbody fusions will be clarified in the near future as well.

This episode, however, is disturbing. It took us several years to get even the minimum clarification from Burkus et al. that eventually appeared in letter format in 2010. This belated information, that the RE rate was higher in an RCT comparing rhBMP-2 versus controls, illuminated otherwise confusing 8-year old FDA data. This revelation also spurred the investigation by Carragee et al. [2] reported here. We hope that an improved system can be implemented to verify or rapidly resolve future discrepancies between the FDA (or other administrative data) and data in published articles from the same studies.

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Clinical Study

Complications with recombinant human bone morphogenetic protein-2 in posterolateral spine fusion associated with a dural tear

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Abstract

BACKGROUND CONTEXT: Potential complications related to ectopic bone formation, as seen with transforaminal lumbar interbody fusion, have always been a concern with the use of bone morphogenetic proteins (BMPs). Although less clearly anticipated, complications related to the proinflammatory effects of recombinant human bone morphogenetic protein-2 (rhBMP-2), such as swelling and edema in the cervical spine, have been observed as well. Until recently, risks related to intradural exposure to BMP have not been widely considered. However, a recent animal study reports "in the presence of a SCI and/or dural tear, rhBMP-2 diffuses intrathecally and activates a signaling cascade in all major CNS cell types, which may increase glial scarring and impact neurologic recovery." Although this study was conducted at the spinal cord level, the observation generates obvious concerns for the much more common scenario of a dural tear associated with lumbar decompression and fusion.

PURPOSE: The purpose of this study was to look for any indication of neurologic injury or impaired neurologic recovery in patients treated with rhBMP-2 for lumbar fusion complicated by dural tear.

STUDY DESIGN/SETTING: Propensity score matched case-control study.

PATIENT SAMPLE: From consecutive series of 1,037 patients who underwent decompression and posterolateral lumbar spine fusion using rhBMP-2/absorbable collagen sponge between 2003 and 2006, intraoperative dural tear was reported in 58 cases (5.59%).

OUTCOME MEASURES: Preoperative and 2-year postoperative Oswestry Disability Index, Short Form-36 (SF-36), leg pain, and back pain scores.

METHODS: Fifty-eight cases in which decompression and posterolateral spinal fusion were complicated by dural tear, where propensity score matched to a group without dural tear, based on age, smoking status, number of surgical levels and preoperative Oswestry Disability Index, SF-36 Physical Composite Summary score, SF-36 Mental Composite Summary (MCS) score, and back and leg pain scores. The patients with a dural tear were then compared with the matched cohort with regard to baseline and 2-year patient-based outcome measures. Particular attention was given to indices of leg pain that might reflect an influence of rhBMP-2 on neurologic function or impaired neurologic recovery.

RESULTS: No patient in the group with a dural tear and three patients in the group without a dural tear complained of new onset radiculopathy postoperatively, with one requiring oral steroids. The radiculopathy resolved within 6 months postoperatively in all three patients. Statistically significant improvement was observed in all health-related quality of life (HRQOL) measures, except SF-36 MCS, at both 1 and 2 years postoperatively in both groups. There were no significant differences in any HRQOL parameter between the groups with or without a dural tear at either 1 or 2 years

postoperatively. In particular, the leg pain improvement, 2.2 points in the group with a dural tear and 2.4 points in the group without a dural tear, was statistically equivalent.

CONCLUSIONS: The data suggests fairly convincingly that the presence of a repairable dural tear is not necessarily an impediment to the use of rhBMP-2 in posterolateral fusion. Further studies are needed to address the less common clinical scenario of BMP use in conjunction with spinal cord injury, as studied in the animal model that prompted this investigation. Finally, avoidance of BMP use may still be prudent in the setting of an unrepairable dural tear.   © 2011 Elsevier Inc. All rights reserved.

Introduction

The clinical application of growth factors involves risks of adverse events, both anticipated and unanticipated. With the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for spinal fusion, anticipated adverse events have included foraminal bone deposition in transforaminal lumbar interbody fusion or posterior lumbar interbody fusion [1–4], and transient osteolysis in both anterior lumbar interbody fusion and transforaminal lumbar interbody fusion applications [5,6]. The risk of unanticipated adverse events is typified by the occurrence of soft-tissue swelling and airway compromise noted after anterior cervical decompression and fusion with rhBMP-2 [7,8].

Among the potential risks considered during preclinical testing for rhBMP-2 in posterolateral fusion was the possibility of bone formation in the epidural space. Meyer et al. [9] demonstrated the safety of rhBMP-2 applied directly to the dural membrane, with and without dural puncture, in a dog laminectomy model. Similar studies with rhBMP-7, including a protocol with direct implantation in the subarachnoid space, also suggested little risk for neurologic injury [10–12]. Thus far, the available clinical experience has been consistent with the preclinical data, in that neurologic complications secondary to intradural BMP exposure have not been reported.

In contrast to the prior literature, a recent animal study has suggested that rhBMP-2 use in the setting of spinal cord injury (SCI) might result in intrathecal penetration and impact neurologic recovery [13]. Although rhBMP-2 use in the setting of SCI may be relatively infrequent, the work of Dmitriev et al. also reintroduces questions regarding the much more common scenario of dural tear associated with a lumbar decompression and fusion. Based on this concern, the purpose of this study was to look specifically for any indication of neurologic injury or impaired neurologic recovery in patients treated with rhBMP-2 for lumbar fusion complicated by dural tear.

Methods

We reviewed the medical records for a consecutive series of 1,037 patients who underwent decompression and posterolateral lumbar spine fusion using rhBMP-2 between 2003 and 2006. Intraoperative dural tear was reported in 58 cases (5.59%), and this cohort forms the basis of the present study. The surgical procedures were performed by six fellowship-trained spine surgeons at a single tertiary spine center. The surgical technique has been reported elsewhere and included the routine use of a suprafascial drain [14,15]. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge (INFUSE bone graft; Medtronic, Minneapolis, MN, USA) was prepared according to standard manufacturer's instructions and wrapped around graft extenders or fillers as previously described [16]. Patients with interbody fusion were excluded.

Demographic data included age, gender, smoking history, comorbidities, and diagnoses. Surgical data included operative time, estimated blood loss, fusion levels, as well as the quantity of rhBMP-2 and other graft materials. The use of tissue sealants after dural repair was also determined, based on both the operative report and hospital billing records. Perioperative data consisted of wound drain output, number of days in the intensive care unit or transitional care unit, overall length of stay, and discharge distribution. New complaints of radiculopathy postoperatively, before discharge, and at the initial postoperative visit was noted. The administration of steroids in the perioperative period was also noted.

Health-related quality of life (HRQOL) measures were collected preoperatively and at standard postoperative intervals. These measures included the Oswestry Disability Index [17], Medical Outcome Study Short Form-36 (SF-36) [18], and numeric rating scales for back pain and leg pain [19].

A matched cohort analysis was performed comparing patients with and without dural tear. Fifty-eight cases in which decompression and posterolateral spinal fusion were complicated by dural tear were propensity score matched [20] based on age, smoking status, number of surgical levels, and preoperative Oswestry Disability Index, SF-36 Physical Composite Summary score, SF-36 Mental Composite Summary (MCS) score, and back and leg pain scores. The patients with a dural tear were then compared with the matched cohort with regard to baseline and 2-year patient-based outcome measures. Patients in whom the dural repair was or was not augmented by sealant were also compared. Particular attention was given to indices of leg pain, which might reflect an influence of rhBMP-2 on neurologic function or impaired neurologic recovery.

Results

Of the 58 patients with an intraoperative dural tear, complete baseline and 2 years HRQOL outcome measures were

Table 1
Summary of demographic preoperative HRQOL scores and surgical data

Variable	No dural tear	Dural tear	p Value
N	51	51	
Age, y	59.5	60.2	.762
Male, N (%)	18 (35)	21 (41)	.684
Smokers, N (%)	10 (20)	7 (14)	.596
Worker's compensation, N (%)	7 (14)	6 (12)	1.000
Length of symptoms, mo	24.7	18.1	.730
ORT, min	251.6	287.3	.030
EBL, cc	736.8	940.2	.135
Total drain output, cc	221.5	225.2	.959
Repaired with sealant, N (%)	NA	29 (57)	NA
Number of levels	1.8	1.9	.312
Postoperative radiculopathy, N (%)	3 (6)	0	.243
Postoperative steroids, N (%)	1 (2)	0	1.000
Preoperative HRQOL			
ODI	51.7	51.7	.991
Back pain	7.8	7.3	.232
Leg pain	8.0	7.8	.713
SF-36 PCS	27.1	27.1	.984
SF-36 MCS	36.7	36.9	.940

HRQOL, health-related quality of life; ORT, operative time; EBL, estimated blood loss; NA, not available; ODI, Oswestry Disability Index; SF-36, Short Form-36; PCS, Physical Composite Summary; MCS, Mental Composite Summary.

available in 51 patients. These 51 patients were propensity score matched, and the preoperative demographic and HRQOL parameters are listed in Table 1. The dural tear group had a mean age of 60 years and was predominantly female (59%). Fourteen percent of the group were smokers. Mean preoperative Oswestry Disability Index score was 51.7 points, and mean preoperative SF-36 Physical Composite Summary score was 27.1 points.

All patients underwent lumbar decompression and instrumented posterolateral fusion with rhBMP-2/absorbable collagen sponge. The groups were matched for number of levels fused (mean 1.9 levels). There was a significantly longer operative time in the group with a dural tear (287 vs. 252 minutes, p=.030) and greater estimated blood loss (940 vs. 737 cc, p=.135) that was not significantly significant. Application of tissue sealant (TISSEAL; Baxter, Deerfield, IL, USA) after dural repair was documented in 36 of 51 cases.

Postoperative wound drain output was equivalent in the two groups. None of the patients required secondary placement of a lumbar drain related to cerebrospinal fluid leak. Postoperatively, there were three patients in the group with a dural tear who complained of new onset radiculopathy. Only one of these patients had radiculopathy severe enough to warrant administration of oral steroids. In all these three patients, the radiculopathy resolved within 6 months postoperatively.

The groups were also matched for preoperative HRQOL scores. Statistically significant improvement was observed in all HRQOL measures, except SF-36 MCS, at both 1 and 2 years postoperatively in both groups (Table 2). There were no significant differences in any HRQOL parameter between the groups with or without a dural tear at either 1 or 2 year postoperatively. In particular, the leg pain improvement, 2.2 points in the group with a dural tear and 2.4 points in the group without a dural tear, was statistically equivalent (p=.612). There were also no differences in HRQOL measures based on whether tissue sealant was applied after the dural repair.

Discussion

Complications related to ectopic bone formation have always been a concern with the use of BMP [1–4]. Although less clearly anticipated, complications related to the proinflammatory effects of rhBMP-2 have been observed as well. The most evident example has been swelling and edema associated with rhBMP-2 use in the cervical spine [7,8]. In general, risk related to intradural exposure to BMP has not been widely considered as an important clinical issue. Preclinical studies implied relative safety [9,11,12], and none of the available clinical data has contradicted this assumption [21,22].

The work of Dmitriev et al. [13], examining the use of rhBMP-2 in an animal model of SCI, challenges this assumption of safety. They report that "in the presence of a SCI and/or dural tear, rhBMP-2 diffuses intrathecally

Table 2
Summary of 1-year and 2-year HRQOL scores and surgical data

HRQOL	No dural tear	Dural tear	p Value
One-year HRQOL			
ODI	35.3	34.3	.828
Back pain	4.6	4.6	.982
Leg pain	5.2	5.0	.733
SF-36 PCS	35.3	34.6	.748
SF-36 MCS	38.6	43.8	.097
Two-year HRQOL			
ODI	35.3	38.0	.528
Back pain	5.0	5.1	.760
Leg pain	5.6	5.6	.946
SF-36 PCS	33.9	34.3	.838
SF-36 MCS	40.6	41.7	.698

HRQOL, health-related quality of life; ODI, Oswestry Disability Index; SF-36, Short Form-36; PCS, Physical Composite Summary; MCS, Mental Composite Summary.

and activates a signaling cascade in all major CNS cell types, which may increase glial scarring and impact neurologic recovery." Although their study was conducted at the spinal cord level, their observations generate obvious concerns for the much more common scenario of a dural tear associated with lumbar decompression and fusion. In particular, the question of whether intradural BMP could limit nerve root level recovery after decompression or exacerbate radicular symptoms seems evident.

The results of the present study suggest that the use of rhBMP-2 in posterolateral fusion does not adversely affect postoperative leg pain in patients with dural tears, in a clinically relevant manner. There were no differences in leg pain scores, or any other HRQOL outcome measure, between the dural tear group and the match controls. The number of patients with preoperative neurologic deficit was too small to determine whether patients with a dural tear had a differential rate of neurologic recovery.

It is not really clear whether these observations imply that intradural exposure to rhBMP-2 in the lumbar spine is inherently safe or that dural repair effectively blocks intradural exposure. In most cases, the dural repair was augmented with a tissue sealant, which prior experience suggests to be an effective mechanical block to BMP diffusion [23,24]. Although the decision to use a sealant may be biased by the extent of the dural tear, there was no apparent difference in outcomes between patients in whom the dural repair was or was not augmented by sealant.

Weakness of this study includes the fact that the extent of the dural tear and the quality of the repair were not definitively quantified. Similarly, the details of tissue sealant application were not well defined. It is presumed that rhBMP-2 application was undertaken after the tear was repaired and sealed, but exceptions may have occurred. Our primary measure, leg pain scores, is a better measure for root inflammation as opposed to inhibition of neurologic recovery. Finally, the risk of rare catastrophic or idiosyncratic effect cannot be detected because of the small sample size.

Despite these shortcomings, the data suggests fairly convincingly that the presence of a repairable dural tear is not necessarily an impediment to the use of rhBMP-2 in posterolateral fusion. Further studies are needed to address the less common clinical scenario of rhBMP-2 use in conjunction with SCI, as studied in Dmitriev's animal model. Finally, avoidance of BMP use may still be prudent in the setting of an unrepairable dural tear.

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Clinical Study

Promoting fusion in minimally invasive lumbar interbody stabilization with low-dose bone morphogenic protein-2—but what is the cost?

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Abstract

BACKGROUND: Using bone morphogenic protein (BMP) to augment fusion in spine surgery is widespread and lends itself in particular to minimally invasive lumbar fusion, where the surface area for fusion is significantly less than the equivalent open procedure.

PURPOSE: Here we described the use of very low–dose BMP in promoting fusion in minimally invasive lumbar interbody fixation but also highlight some of the potential complications of BMP-2 use and techniques available to reduce or avoid them.

STUDY DESIGN: Prospective observational study of consecutive patients undergoing minimally invasive lumbar interbody fusion with percutaneous pedicle screws.

PATIENT SAMPLE: Thirty patients aged between 22 and 78 years (mean 53 years).

OUTCOME MEASURES: Thin-slice lumbar computed tomography scanning with multiplanar reconstruction at 6 and 12 months postoperative.

METHODS: Thirty-six spinal levels were instrumented in total, of which four underwent posterior lumbar interbody fusion and 32 underwent transforaminal lumbar interbody fusion. Bone graft harvested locally was placed in the disc space with low-dose BMP-2 (1.4 mg per level).

RESULTS: Thirty-three of 36 spinal levels showed complete fusion at a mean postoperative scan time of 7.1 months. Two levels demonstrated partial fusion at 6 months, which was complete at 12 months. There was one case of nonunion at 12 months, which also demonstrated vertebral body osteolysis. Despite very low–dose BMP-2, two cases of asymptomatic heterotopic ossification were observed, and there were two cases of perineural cyst formation, one of whom required revision of the interbody cage.

CONCLUSIONS: The use of BMP with autograft in the disc space during minimally invasive lumbar interbody fusion is associated with a high rate of early fusion. Even with very low–dose BMP used in this study, complications related to BMP usage were not avoided completely. © 2011 Elsevier Inc. All rights reserved.

Keywords: Minimally invasive; Fusion; BMP; Complications

Introduction

The use of minimally invasive techniques to perform lumbar interbody fusion with percutaneous pedicle screws is well described [1–3]. The potential advantages of the minimally invasive versus an open approach are a reduction in tissue trauma with quicker patient recovery, less postoperative pain, and minimization of blood loss, although there is some skepticism over the clinical importance of these differences and whether they significantly outweigh the potential risks and learning curve associated with a minimally invasive approach [4]. As well as concerns over screw placement accuracy and radiation exposure, there are

EVIDENCE & METHODS

Context
rhBMP-2 has been used in an off-label manner in the United States for PLF, PLIF, and TLIF applications. The authors report results using local autograft with a relatively small dose of rhBMP-2 within an interbody cage in patients undergoing a minimally invasive TLIF or PLIF.

Contribution
In this case series, high fusion rates are reported when a surgical approach that consisted of posterior instrumentation, careful end plate preparation, interbody cage placement, local autograft, and rhBMP-2 in low doses was used. Despite the lower dosage, complications associated with rhBMP-2, namely osteolysis, heterotopic ossification, and cyst formation were observed in 5 of 30 patients (17%, 95% CI 7%, 27%), one of whom required additional surgery.

Implication
This technique appears to afford satisfactory and possibly accelerated interbody fusion. Complications associated with rhBMP-2 remain common but may be less frequently seen compared with higher doses. Furthermore, questions remain regarding clinical outcomes, safety, and cost compared with simpler, and possibly equally effective, methods.

—*The Editors*

long-term concerns over whether minimally invasive interbody stabilization with percutaneous pedicle screws can achieve solid bony fusion in the absence of posterolateral intertransverse bone grafting, a routine component of the open procedure for most surgeons. Although fusion per se does not seem to be a prerequisite for good clinical outcome [5–7], if minimally invasive interbody fusion was associated with a higher rate of pseudoarthrosis than traditional methods, this would add to the list of reasons not to adopt the less invasive approach. The arrival of recombinant bone morphogenic protein (BMP), particularly BMP-2 (Infuse, Medtronic, Memphis, TN, USA), into the surgical armamentarium has provided a genuinely osteoinductive agent in fusion surgery, and the ability of BMP to augment fusion in the lumbar spine is widely described for both anterior and posterior surgery [8–14]. However, there have been concerns over the incidence of heterotopic bone formation in both the instrumented disc space and the related nerve root foramina [10], as well as acute inflammatory changes around the nerve root [15]. This has raised the possibility of BMP improving rates of bony fusion but creating a new range of iatrogenic and potentially symptomatic problems for the patient. Here, we describe our experience with minimally invasive lumbar interbody fusion using low-dose BMP-2, looking at rates of fusion while also highlighting complications thought to be related to BMP usage.

Methods

Thirty patients (16 female, 14 male) aged between 22 and 78 years (median 51 years) underwent surgery between November 2007 and July 2009. All patients underwent minimally invasive fusion surgery involving the insertion of percutaneous pedicle screws (either Sextant or Longitude; Medtronic, Memphis, TN, USA) in the lumbosacral spine, together with interbody fusion through a minimally invasive operating tube system (Metrx; Medtronic, Memphis, TN, USA). Twenty-four patients underwent surgery at a single spinal level, whereas six patients underwent surgery at two adjacent spinal levels (36 levels in total). A transforaminal lumbar interbody fusion (TLIF) procedure with a single cage was performed at 32 levels, with a posterior lumbar interbody fusion (PLIF) procedure at the other four levels.

Surgical technique

After administration of general anesthetic and positioning in the prone position, a computerized navigation system reference array (Stealth Station; Medtronic, Louisville, CO, USA) was placed percutaneously into the posterior iliac crest. Radiographic images of the surgical levels were then obtained and uploaded to a surgical navigation system (Stealth Station; Medtronic). These images were acquired using either a three-dimensional fluoroscope (O-arm; Medtronic, Louisville, CO, USA) or by merging standard anteroposterior and lateral intraoperative fluoroscopic images with a preoperative computed tomography scan (Fluoromerge; Medtronic, Louisville, CO, USA). Pedicle screws and interbody cages were then positioned using a percutaneous, image-guided Seldinger technique, without further requirement for intraoperative imaging.

Decompression and interbody fusion

For TLIF, the decompression was performed using a tubular dilator system (Metrx; Medtronic, Memphis, TN, USA) on the most symptomatic side, after pedicle screws had been inserted on the other side. This largely followed a technique previously described [3] but in addition used the navigation system to guide the placement of the operating tube and the screws. During the decompression, autograft from the facet joint with or without lamina was harvested to be used to pack the disc space along with BMP. The disc space was prepared by incising the annulus and sequentially inserting a series of lordotic distractors. Once the disc space was maximally distracted, a rod was inserted percutaneously on the contralateral side and locked onto the two pedicle screws already in situ, thereby maintaining distraction. The disc distractor was then removed,

and the end plates were prepared. The smallest commercially available dose of BMP-2 (4.2 mg) was soaked into a collagen sponge. One-third of the total was used per level fused (approximately 1.4 mg BMP-2). This was divided into two, with half (0.7 mg) inserted into the anterior disc space with bone graft and the other half (0.7 mg) inserted into the cage along with more local bone graft for TLIF (Capstone; Medtronic, Memphis, TN, USA). For PLIF procedures, 1.4 mg of BMP was soaked onto a collagen sponge and packed into the anterior disc space along with local bone graft before insertion of the cages (R90; Medtronic, Memphis, TN, USA). Further bone graft but not BMP-2 was then packed around the cages. Cages were recessed as much as was felt to be safe, usually 2 to 5 mm from the posterior edge of the superior end plate, using the navigation system to confirm positioning.

Assessment of fusion

Postoperatively, all patients underwent computed tomography scans of the lumbar spine with reconstruction in sagittal and coronal planes, to assess the degree of fusion across the disc space. The initial scan was done at approximately 6 months from surgery. Fusion was graded based on criteria modified from a method previously described [16] and agreed locally with a radiologist. The degree of fusion was then independently reported by a blinded radiologist and surgeon. Complete fusion was described if trabecular bone was seen to bridge the disc space, with accompanying remodeling of the cortical end plates (Fig. 1, Top). Partial fusion was described if trabecular bone could be seen extending from the end plate into the disc space, but the bridge was not complete (Fig. 1, Middle). Absent fusion was described if the disc space demonstrated no evidence of trabecular bone formation extending from the end plates (Fig. 1, Bottom). If evidence for fusion was considered to be incomplete or absent, a further scan was arranged at 12 months.

Results

In total, 36 spinal levels were operated on in 30 patients using bone graft and BMP-2 (1.4 mg per level). Table 1 outlines their clinical indications for fixation. Of 36 spinal levels in total, there were four PLIFs and 32 TLIFs (Table 2).

Degree of fusion

Computed tomography imaging revealed that for 33 operated levels, complete bony fusion was observed at the first postoperative scan (mean 7.1 months). Two further patients who had undergone two-level fixation demonstrated complete fusion at one level and partial fusion at the other level at 6 months, which was complete at 12 months. In one patient, there was no evidence of fusion at 12 months, where osteolysis and cage subsidence into the end plate were also observed. Despite this, the patient was
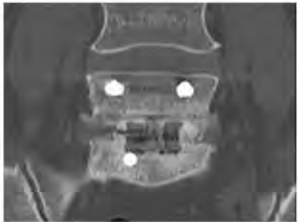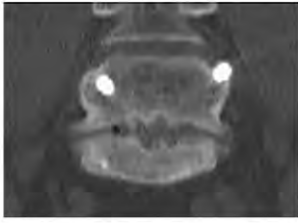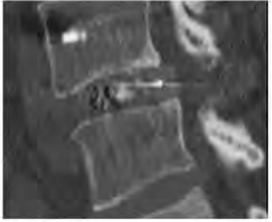
	Coronal	Sagittal
Grade I - complete fusion: Trabecular bone was seen to bridge the disc space, with accompanying remodeling of the cortical end plates		
Grade II - partial fusion: Trabecular bone seen extending from the end plate into the disc space, but forming an incomplete bridge		
Grade III - no fusion: No evidence of trabecular bone formation extending from the end plates		

Fig. 1. Classification of fusion based on postoperative computed tomography imaging.

Table 1
Lumbar canal pathology within the series

Pathology	No of patients
Central canal stenosis	
With spondylolisthesis	4
Without spondylolisthesis	0
Foraminal stenosis/collapse	
With spondylolisthesis	14
Without spondylolisthesis	6
Discogenic back pain and disc prolapse	
With radicular pain	6
Without radicular pain	0
Total	30

symptomatically improved compared with their preoperative status, and so the cage was not revised.

Complications

Two cases (one PLIF, one TLIF) of heterotopic ossification in the neural foramen were observed on postoperative imaging. One of these patients is depicted in Fig. 2. In both patients, preoperative symptoms of severe radicular leg pain had resolved and neither reported postoperative leg pain, which could be attributed to the heterotopic ossification seen on computed tomography scanning.

A further patient presented preoperatively with severe L4 radiculopathy secondary to a Grade I degenerative spondylolisthesis that resolved completely after TLIF. Two months after surgery, she underwent a postoperative magnetic resonance imaging as part of another study looking into extent of minimally invasive canal decompression. This investigation demonstrated good decompression of the central canal and foramen but also revealed a large inflammatory cyst in the neural foramen on the operated side, causing significant displacement of the nerve root (Fig. 3). Despite this, the patient's symptoms of leg pain in an L4 distribution had resolved (preoperative visual analog scale score 8/10 to postoperative visual analog scale score 1/10). We have continued to follow this patient, and she has remained asymptomatic.

One patient developed a recurrence of their preoperative radicular pain 4 weeks post-op. Preoperatively, he had presented with severe L4 radiculopathy and a Grade I degenerative spondylolisthesis. The lower limb pain resolved completely after surgery. When his pain recurred, magnetic

Table 2
Surgical details

Surgical level	TLIF	PLIF
L3/L4	2	0
L4/L5	16	1
L5/S1	14	3

TLIF, transforaminal lumbar interbody fusion; PLIF, posterolateral lumbar interbody fusion.

resonance imaging demonstrated a degree of cage retropulsion into the foramen. Associated with this was a large inflammatory cyst, similar to that seen above, which was compressing the L4 nerve root. It could not be determined whether the recurrent radicular pain occurred as a consequence of the cage or the cyst, although the cage did not seem to be causing significant root compromise. The case was revised whereby the cage was reinserted into the disc space and the cyst drained, with a resolution in radicular symptoms.

As mentioned above, there was one case of vertebral body osteolysis, cage subsidence, and nonunion in a patient with no preoperative risk factors for this complication. Surgical technique was no different to other cases, with good end plate preservation during disc removal and maintained distraction during insertion of the cage. This patient had presented with radiculopathy, which was significantly improved, and there, postoperative back pain was managed conservatively.

Discussion

Although debate continues over the role of fusion surgery in the management of patients with back pain alone, there is consensus agreement that decompression with fusion is beneficial in the surgical management of conditions such as isthmic spondylolisthesis with radiculopathy because of foraminal root compression, or in cases of degenerative spondylolisthesis with neurogenic claudication from canal stenosis. This view was supported in a recent prospective study [17]. Although the primary outcome in all of these procedures is improvement in clinical symptoms, the surgical goals are first to achieve adequate decompression of the neural elements and second to maintain decompression and prevent progressive deformity through successful fixation and fusion. For posterior surgery, pedicle screw systems have become extremely popular over the last 10 years, supplementing posterolateral and intertransverse bone grafting. Interbody fusion with bone graft and prosthetic cages has also gained in popularity, allowing for greater distraction of the disc and nerve root foramen, maintenance of foraminal height, increased fusion interface, and reduced cantilever stresses on posterior instrumentation, at the potential cost of increased blood loss, manipulation of the thecal sac and nerve roots, and longer operative time [18]. Over the last 5 years, minimally invasive methods of lumbar pedicle screw placement and interbody fusion have been described [3], with potential advantages to the patient in terms of intraoperative blood loss, postoperative pain, and recovery from surgery. However, a potential disadvantage of these techniques is that placing pedicle screws through a true percutaneous (as opposed to an open or "mini-open") technique negates the ability to perform posterolateral bone grafting, and one is, therefore, reliant on the efficacy of interbody fusion alone. This study demonstrates that with the use of locally harvested bone graft and a low dose of BMP (1.4 mg) in the interbody space,
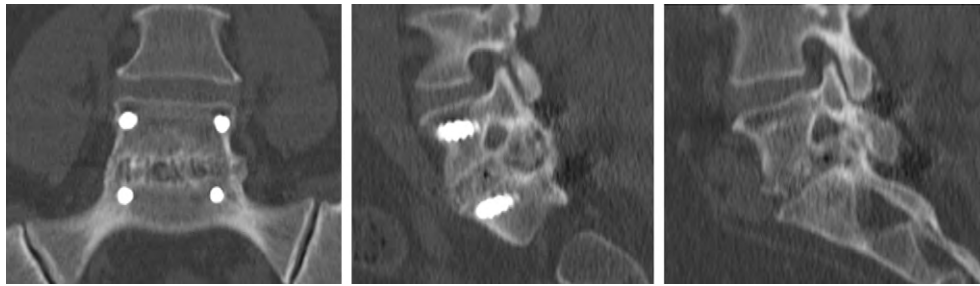
Fig. 2. Magnetic resonance imaging images from a patient who underwent L5/S1 minimally invasive transforaminal lumbar interbody fusion. (Left) The disc space demonstrates solid bony fusion with trabecular bone formation and end plate remodeling at 6 months. (Middle, Right) Heterotopic ossification can be observed within the lateral recess and nerve root foramen. This was not associated with radicular symptoms.

almost all cases will achieve the surgical goal of fusion within a few months of surgery. This has been seen in previous studies when higher doses of BMP were used (4.2 mg) [10] and has proven more effective than our experience with iliac crest bone graft alone in minimally invasive cases (unpublished data, Nowitzke & Wood, 2009).

That the use of BMP-2 is associated with a high rate of early postoperative fusion in this series is not surprising given what is already known about the osteoinductive properties of this compound, although the dose used in this study was at least 50% lower than previously published series in the lumbar spine. Human recombinant BMP exists in two forms—BMP-2 and BMP-7, with evidence that BMP-2 may be more effective than BMP-7 in promoting fusion when both are compared with bone graft alone [12,19]. Multiple studies have now demonstrated improvements in fusion in lumbar spine surgery when BMP has been compared with autograft and allograft, with and without pedicle screws. Not only does fusion occur more quickly, but also the rate of pseudoarthrosis is significantly reduced [9]. Of equal interest is the significant clinical improvement seen in a number of studies comparing BMP with bone graft with bone graft alone [9,20]. One factor implicated is the avoidance of morbidity from the iliac crest after bone harvesting that may contribute to a poor patient experience and a worse clinical outcome, negated when BMP is used with local bone. The growing body of data regarding the utility of BMP in promoting fusion supports an expanding role in fusion surgery in the future, particularly in difficult cases of multilevel surgery or pseudoarthrosis/failed fusion. There are, however, two obstacles to its more widespread use—cost, particularly in publicly funded health-care systems and adverse effects, reports of which are becoming more common.

Cost in surgery can be difficult to measure because of the number of variables that could change as a consequence of using BMP. Certainly, the cost of a single dose of BMP adds a significant amount to the expense of surgery that is not immediately offset in savings on other intraoperative products, and studies comparing the cost versus quality-of-life improvement per patient have suggested that although BMP-2 use in spine surgery is effective when compared with bone graft, cost-effectiveness is likely to

be low [19]. However, others have argued that the upfront costs of BMP are more than offset by subsequent savings in areas, such as postoperative pain management, reduced hospital stay, and postoperative rehabilitation, all achieved through the avoidance of iliac crest graft morbidity [21,22]. Unwanted effects of BMP largely fall into three groups: heterotopic bone formation; osteolysis from local osteoclast activation; and postoperative soft-tissue inflammation and swelling. Heterotopic bone formation has been observed with BMP-2 both in open posterolateral fusion [23,24] and minimally invasive posterior fusion [10], where epidural bone formation was witnessed in 20% of BMP cases versus 8% of cases, where bone graft alone was used, although no clinical sequelae were seen. At least 4.2 mg BMP-2 per spinal level was used in these studies. A more recent study observed four cases of heterotopic ossification with associated neurological symptoms, although 12 mg of BMP-2 was used per level, almost a magnitude of order more than in the present study [25]. Lysis within the vertebral body and cage loosening have also been reported in five of 68 patients undergoing PLIF with the use of BMP-2 [26], although other series have reported end plate resorption in almost all cases of cervical and lumbar interbody fusion using BMP [27]. Osteolysis typically presents 6 to 12 weeks after surgery, with back pain that is self-limiting. Soft-tissue swelling has commonly been seen with BMP-2 usage, particularly in the cervical spine, where this complication can be life threatening [28]. Largely, these complications are thought to be dose related. Theoretically, containment of BMP both within the anterior disc space and within the prosthesis are likely to reduce exposure of the neural structures to the compound, and care taken during end plate preparation to avoid end plate fracture or perforation may reduce the rate of vertebral body osteolysis. Adequate recession of the cage beyond the posterior end plate margin may be a further important factor in reducing intracanalicular BMP-related complications [10].

Despite the use of very low–dose BMP-2 in this series, we have still observed heterotopic ossification in two patients (6.6%), perineural inflammatory cyst formation in two (6.6%), and vertebral body osteolysis with nonunion in one patient (3.3%), even when BMP-2 has been placed
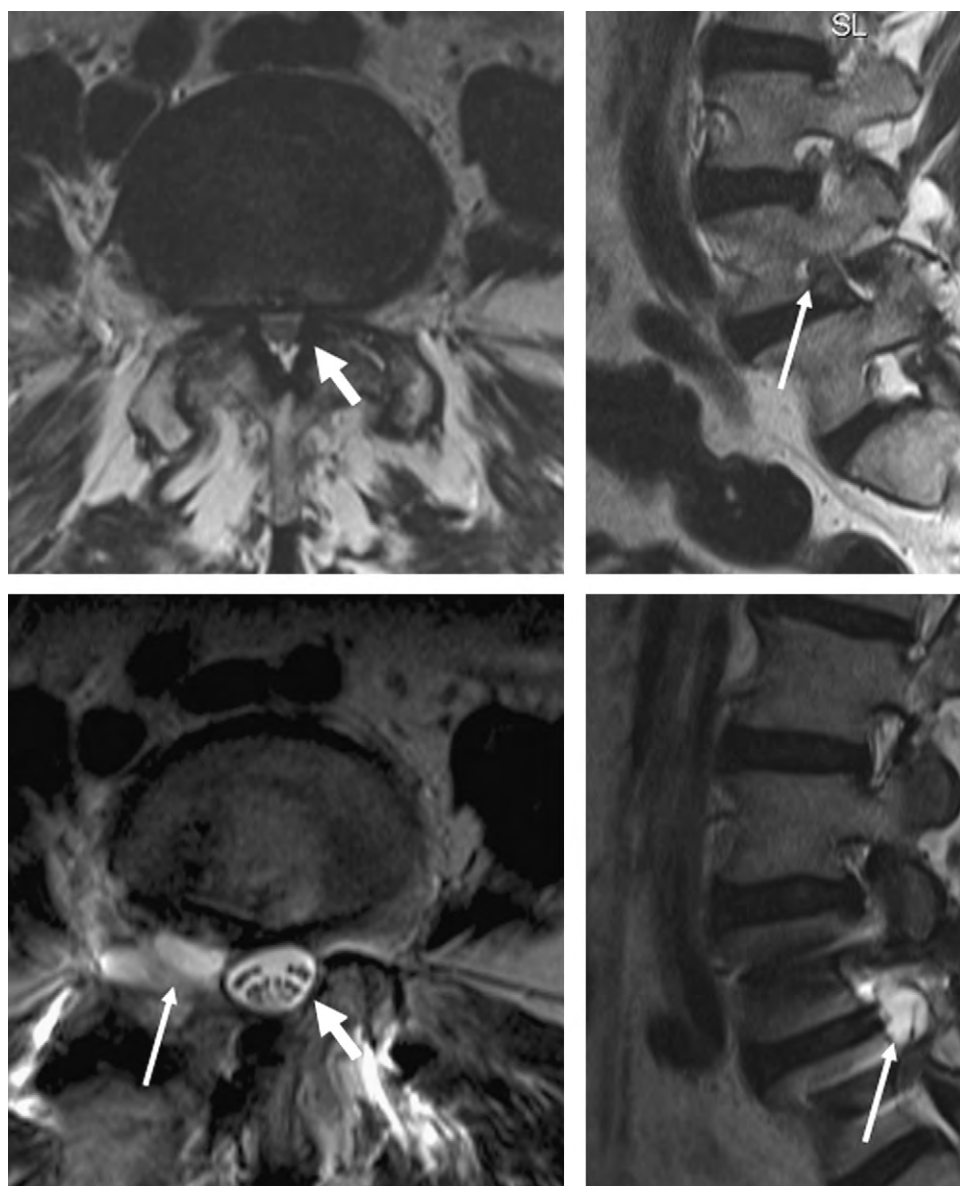
Fig. 3. Magnetic resonance imaging images from a patient with a Grade I degenerative spondylolisthesis who underwent L4/L5 minimally invasive transforaminal lumbar interbody fusion. (Top Left, Top Right) Severe central canal stenosis (thick arrow) can be seen along with severe right L4 foraminal stenosis and nerve root compression (thin arrow). (Bottom Left, Bottom Right) Although the central canal and foramen are successfully decompressed (thick arrow), a large cyst has formed within the L4 root foramen (thin arrow). This was not causing radicular pain.

exclusively within the anterior disc space and prosthesis. Although some of these complications were not symptomatic, as has been seen previously [10], they are all likely to be BMP related. Thus, the overall clinical complication rate from very low−dose BMP-2 use is low, and one could use this to support its off-label use in minimally invasive posterior lumbar fusion. Equally, given that high rates (90% at 1 year) of interbody fusion can be achieved minimally invasively without using this compound [10], one could argue that the combination of added cost and potential morbidity should limit its use to complex cases, where risk factors for nonunion are high. We would, however, suggest that given that many of the complications associated with off-label

BMP-2 use in spine surgery are dose related, the low dose used in this study is perfectly adequate to promote early fusion and is likely to produce fewer BMP-2−related complications.

Conclusions

At a dose lower than that previously described, we have demonstrated a high-fusion rate with BMP-2 and local bone graft for minimally invasive lumbar interbody fusion. Moreover, posterolateral grafting does not seem to be a requirement for lumbar segmental fusion with pedicle screws. However,

despite this very low-dose use, we have still observed complications attributable to BMP-2 use. The future market for BMP-2 in lumbar fusion surgery will depend on the clinical significance of increased fusion in the context of possible side effects and cost considerations, as well as the potential arrival of newer and safer fusion-promoting agents.

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Clinical Study

Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest

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Abstract

BACKGROUND CONTEXT: Considerable debate exists regarding the incidence of persistent pain from the iliac crest bone graft (ICBG) harvest site. Different study designs have led to a variety of reported rates.

PURPOSE: The purpose of this study was to determine the incidence and severity of bone graft site pain after iliac crest harvest.

STUDY DESIGN: Cross-sectional.

PATIENT SAMPLE: One hundred and twelve patients, who had a posterior lumbar fusion, seen at a tertiary spine center for a routine postoperative visit.

OUTCOME MEASURES: Numeric rating scales (0–10) for pain over lower back, right, and left posterior iliac crests.

METHODS: An independent investigator, not directly involved in the care of the patient and unaware of the type of bone graft used in the fusion, examined the patient for tenderness over the surgical site as well as the left and right posterior iliac crest. After the examination, data on the source of grafting material, complications during harvest, and backfilling of the graft site defect were collected from the medical records. The patients were then classified as to whether ICBG was harvested or not. Chisquare test was used to determine any difference in the proportion of iliac crest pain between the bone graft group and no bone graft group. Correlations between body mass index (BMI), time since surgery, and the incidence and severity of bone graft site pain were also determined.

RESULTS: There were 72 women and 40 men with a mean age of 56.6 years (range, 16–84). Mean follow-up was 41 months (range, 6–211 months) with a median of 25 months. Iliac crest bone graft was harvested in 53 (47.3%) patients through the midline incision used for lumbar fusion. In 59 patients (52.7%), recombinant human bone morphogenetic protein-2 was used with no graft harvest. There was no statistically significant difference in the proportion of patients complaining of tenderness over both or either iliac crest between the two groups. Only 10 patients had pain over the same crest from which the graft was harvested. No correlations between number of levels fused, levels fused, BMI, length of follow-up, and the incidence and severity of bone graft site pain were seen.

CONCLUSIONS: The results of this study highlight the difficulty in differentiating pain originating from the graft site versus residual low back pain. The incidence of pain over the iliac crest was similar in patients in which iliac crest was harvested and those in which no graft was harvested.   © 2011 Elsevier Inc. All rights reserved.

Keywords: Iliac crest graft; Bone grafting; Donor site pain; Posterior iliac crest; Lumbar fusion

EVIDENCE & METHODS

Context
Avoidance of iliac crest bone graft (ICBG) site pain is one of the motivations for the use of bone graft substitutes in lumbar fusion. Some studies purport persistent pain problems in 30%–40% of patients after posterior ICBG. This study aimed to assess whether pain over the posterior iliac crest region, postoperatively, is more common in patients who have had graft harvested for short segment lumbar fusion than those who did not.

Contribution
The authors found high rates of persistent pain at potential harvest sites in the entire group. Independent, blinded examination at an average of 2-years follow-up showed the incidence of posterior crest pain following lumbar fusion was similar between patients who had ICBG harvesting performed and those who received rhBMP-2.

Implication
The authors point out the limitations of the study, including possibly being underpowered to detect small differences between groups. That said, the results certainly suggest the prevalence of bone graft site morbidity, attributable to harvesting for lumbar surgery, is much less than commonly supposed or is similar to pain processes induced by rhBMP-2. The use of bone graft replacements (especially bone growth factors with inflammatory or neuritis potential) to avoid a suspected high morbidity of ICBG harvesting in short segment fusion should be reconsidered.

—The Editors

Introduction

Autogenous bone graft harvested from the posterior iliac crest to achieve fusion has traditionally been the standard of care for patients undergoing lumbar arthrodesis. However, this procedure is not without problems. Numerous studies have cited the incidence of both major and minor complications associated with harvesting bone from the posterior iliac crest [1–7]. Some patients also report of residual pain from the bone graft site [4,5,8–17]. Bone graft substitutes have been introduced to obviate both the risk of complications and as a solution for the residual pain attributed to harvesting of ICBG [18–20]. However, considerable debate exists regarding the incidence of persistent pain from the iliac crest bone graft (ICBG) harvest site. Different study designs have led to a variety of reported rates [4,5,8–17]. Randomized clinical trials of lumbar fusion comparing ICBG to bone graft substitutes have shown no difference in clinical outcome measures such as the Oswestry Disability Index, Short Form-36, and rating scales for back and leg

pain [9,18,19]. However, the incidence of bone graft pain was specifically sought and reported only in the ICBG group and not in the bone graft substitute group, such that the incidence of iliac crest site pain in patients who underwent fusion is unknown. The purpose of this study is to determine the incidence and severity of bone graft site pain after instrumented posterolateral lumbar fusion with and without iliac crest graft harvest.

Methods

Patients seen at the Norton Leatherman Spine Center on a routine postoperative visit who had an instrumented posterolateral fusion done at one to two levels from L1 to S1 were included in the study. Patients who had a possible or definite pseudoarthrosis based on imaging studies or had fusion extending into the thoracic spine were excluded. An independent investigator, not directly involved in the care of the patient and unaware of the type of bone graft used in the fusion, examined the patient for tenderness over the surgical site as well as the left and right posterior iliac crest. The patients were asked to rate the intensity of the pain with direct palpation over each crest on a scale of 0 to 10 with 0 being no pain and 10 being the worst pain experienced.

There is no scar over the donor graft site in these patients, because the graft is harvested through the midline lumbar incision. The fascia over the iliac crest was incised and the periosteum was lifted. A tricortical window was created using osteotomes, which was then hinged open. The outer table was removed, and cancellous bone was then harvested through the window using curettes. The defect was then packed with Gel-foam (Pfizer, New York, NY, USA). In cases where the outer table was not harvested, the defect was backfilled with a ceramic bone void filler (Pro Osteon; Interpore Cross, Irvine, CA, USA); and the tricortical window was replaced. The fascia was then closed.

After the examination, data on the source of grafting material, complications during harvest, and backfilling of the graft site defect were collected from the medical records. The patients were then classified as to whether ICBG was harvested or not. Chi-square test was used to determine any difference in the proportion of iliac crest pain between the bone graft group and no bone graft group. Correlations between body mass index, time since surgery, and the incidence and severity of bone graft site pain were also determined. For all analysis, the worst score over either iliac crest was used.

Results

One hundred and twelve patients, 72 women and 40 men with a mean age of 56.6 years (range, 16–84) were enrolled. Mean time elapsed since surgery, at the time of examination,

was 41 months (range, 6–211 months) with a median of 25 months. In 59 patients (53%), recombinant human bone morphogenetic protein-2 was used with no graft harvest. In these patients, the incidence of tenderness over either posterior iliac crest was 51% (30 of 59) (Table 1).

Iliac crest bone graft was harvested in 53 (47%) patients through the same midline incision used for lumbar fusion. The incidence of tenderness over either posterior iliac crest in these patients was 57% (30 of 53). Among the 47 patients who had iliac crest harvested from the right side, only 10 (23%) had pain over the right iliac crest. Among the six patients who had iliac crest harvested from the left side, none had pain over the left iliac crest. Thus, only 10 of 53 patients (19%) had concordant pain from the iliac crest graft harvest site.

In both groups, most patients who complained of iliac crest tenderness reported symptoms with palpation over both iliac crests. There was no statistically significant difference in the proportion of patients complaining of tenderness over both or either iliac crest between patients in which bone graft harvest was performed and those who did not (p=.543). The severity of pain on palpation was similar in patients in whom ICBG was harvested (3.8±3.2) and those in whom graft substitute was used (3.6±3.8, p=.745). Six patients who had iliac crest harvest had a backfill of the iliac crest defect using Pro Osteon. There was no difference in the incidence or severity of graft site pain between those whose crest defect was backfilled and those who did not (p=.830).

In the 10 patients with concordant bone graft site pain, the mean pain score was 4.4±2.8 (range, 1–9). No correlations between levels fused (r=−0.039, p=.683), BMI (r=0.194, p=.039), length of follow-up (r=−0.152, p=.107) (Table 2), and the incidence and severity of bone graft site pain were seen. There were no differences in the severity of iliac crest pain between patients who had a one-level versus a two-level fusion (p=.073).

Discussion

Criticisms of previous studies evaluating the incidence of pain from graft site harvest include the lack of blinding and the inadequate assessment of the contralateral iliac crest site [21]. In the present study, we have corrected these shortcomings and determined that the incidence of concordant pain from the iliac crest donor site was 9%. Previous

Table 1
Summary of results

Graft	Posterior iliac crest tenderness				
	None	Left	Right	Both	Total
Graft substitute	29	4	9	17	59
Left ICBG	3	0	1	2	6
Right ICBG	20	3	10	14	47

ICBG, iliac crest bone graft.

Table 2
Mean pain score over iliac crest, 0 being no pain and 10 being the worst pain possible

Follow-up (mo)	N	Iliac graft site pain score
<12	14	3.86
13–23	32	3.53
24–35	27	2.37
36–47	10	3.90
48–59	5	4.00
60–71	8	2.88
72–83	7	3.14
84	9	1.89
Total	112	3.09

mo, months.
In patients with pain over both iliac crests, the more severe pain score was used.

studies looking at the incidence of iliac crest graft pain after fusion surgery included only patients known to have had iliac crest harvest [13,22]. The present study included both patients with and without iliac crest harvest who underwent instrumented posterolateral fusion and showed that even patients who did not have any iliac crest harvested, complained of pain over both iliac crests. Whether or not bone graft was actually harvested, 54% of patients complained of tenderness over the iliac crest, with the majority having tenderness over both crests rather than either one. The present study demonstrated that iliac crest graft site pain can occur even without iliac crest graft harvest and is, thus, a poor marker for graft site morbidity. This lack of specificity implies that posterior iliac crest pain cannot be directly attributable to bone graft harvest alone. Posterior iliac crest pain can be because of a myriad of causes in patients who had posterior lumbar surgery. This includes continued or new lumbar spine pathology with referred pain, postsurgical muscle scarring, radiculitis because of nerve root irritation, and inflammation.

Similar to previous studies [1,10,11,22,23], our data show that it is very difficult to delineate, with certainty, pain from the harvest site as opposed to pain primarily related to the lumbar spine. Robertson and Wray [23] found a greater incidence of graft site pain in patients who had lumbar fusion compared with those fused more proximally. Delawi et al. [22] reported similar findings in that patients whose fusion extended to L3 or more caudally had a greater incidence of graft site pain than those fused proximal to L3.

Although randomized clinical trials showed no difference in clinical outcome measures in patients undergoing lumbar fusion with ICBG compared with those receiving bone graft substitutes [9,18,19], the incidence of bone graft pain was specifically sought and reported only in the ICBG group and not in the bone graft substitute group such that the incidence of iliac crest site pain in patients who underwent fusion without ICBG harvest could not be reported. The results of the present study showed that even in patients in whom no graft was harvested from the iliac crest, the

incidence of tenderness over either posterior iliac crest was 51%.

There are limitations to this study. We were unable to determine the presence and degree of preoperative pain over the crest area. Also, radiographic studies to determine the presence of concomitant sacroiliac disease were not done. The study may be underpowered to detect differences between the groups as the incidence of iliac craft site tenderness in patients who had no graft harvest is unknown and thus an ad hoc power analysis could not be done.

The results of this study highlight the difficulty in differentiating pain originating from the graft site versus residual low back pain. The incidence of pain over the iliac crest was similar in patients in which iliac crest was harvested and those in which no graft was harvested.

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Commentary

Commentary: Iliac crest bone graft: are the complications overrated?

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COMMENTARY ON: Howard JM, Glassman SD, Carreon LY. Posterior iliac crest pain after posterolateral fusion with or without iliac crest graft harvest. Spine J 2011;11:534–7 (*in this issue*).

The authors of the preceding article seek to definitively address the issue of how painful iliac crest site harvest is for patients undergoing posterior lumbar fusion [1]. They designed their study to address some of the shortcomings of prior studies, including palpating both iliac crests for all patients, including patients who had not had bone graft harvested from their crests at all, and having the same midline incision used for harvest in these patients so they would not know which side had been harvested.

Given the less invasive nature of current bone graft harvest compared with historically more extensive harvest, for example, of the entire outer table of the iliac crest, it is reassuring to learn that their study showed that only 19% of their patients had pain over the iliac crest after it had been harvested, at minimum time after surgery of 6 months (ranging from 6 to 211 months, mean 25 months postoperation). Interestingly, of 59 patients without any iliac crest bone graft (ICBG) harvesting, 30 had tenderness over the iliac crest (51%); whereas of 53 patients who actually did have ICBG harvesting, these were equally likely to have tenderness over the untouched ilium as the one that actually was harvested. That is at the time of testing, having had bone graft harvesting did not predict iliac crest pain.

A frequently cited justification for use of artificial bone substitutes, such as bone morphogenetic protein (BMP), is the donor site morbidity. Although no other complications were described in this article, pain is the most common complication reported in most studies of donor site morbidity. This study disputes the severity and frequency of this complaint and puts it in the perspective of the general gluteal area pain experienced by patients after posterior lumbar fusion. Although this study did not assess early pain related to bone graft harvest because their minimum time at follow-up was 6 months, certainly this is within the time frame that patients' postoperative pain diminishes.

Reported fusion rates in single-level posterior instrumented lumbar fusion with ICBG are generally 75% to 95% [2,3] as assessed by a variety of methods. However, in smaller comparison studies between ICBG and BMP, fusion rates from 70% to 86% versus 82% to 96% were observed [4–6], including one study that did not show a significant difference in fusion rates when using BMP versus autograft in patients older than 65 years. Although the comparisons with BMP seem to demonstrate improved fusion rates, the discrepancy varies among studies [7]. Because the fusion rates for these cases can be quite acceptable, it would be important for studies to improve stratification of patients who may have increased risk for pseudoarthrosis, both commonly accepted and less well described and understood, so that surgeons can better weigh the costs of using BMP versus ICBG.

Certainly the present study lends further support to the consideration that the oft-cited "painful iliac crest donor site" is less serious and frequent than BMP enthusiasts would have us believe. Besides the potential benefit of BMP leading to variably higher fusion rates, the incidence of swelling and inflammation, radiculitis, osteolysis, and ectopic bone formation need to be included in the consideration of its use. Given the increasing attention focused on appropriate health care costs, cost benefit considerations for use of BMP should be better directed at those specific patient groups at greater risk for pseudoarthrosis.

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Technical Report

Local bone graft harvesting and volumes in posterolateral lumbar fusion: a technical report

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Abstract

BACKGROUND CONTEXT: In lumbar surgery, local bone graft is often harvested and used in posterolateral fusion procedures. The volume of local bone graft available for posterolateral fusion has not been determined in North American patients. Some authors have described this as minimal, but others have suggested the volume was sufficient to be reliably used as a stand-alone bone graft substitute for single-level fusion.

PURPOSE: To describe the technique used and determine the volume of local bone graft available in a cohort of patients undergoing single-level primary posterolateral fusion by the authors harvesting technique.

STUDY DESIGN: Technical description and cohort report.

PATIENT SAMPLE: Consecutive patients undergoing lumbar posterolateral fusion with or without instrumentation for degenerative processes.

OUTCOME MEASURE: Local bone graft volume.

METHODS: Consecutive patients undergoing lumbar posterolateral fusion with or without instrumentation for degenerative processes of were studied. Local bone graft was harvested by a standard method in each patient and the volume measured by a standard procedure.

RESULTS: Twenty-five patients were studied, and of these 11 (44%) had a previous decompression. The mean volume of local bone graft harvested was measured to be 25 cc (range, 12–36 cc). Local bone graft was augmented by iliac crest bone in six of 25 patients (24%) if the posterolateral fusion bed was not well packed with local bone alone. There was a trend to greater local bone graft volumes in men and in patients without previous decompression.

CONCLUSION: Large volumes of local bone can be harvested during posterolateral lumbar fusion surgery. Even in patients with previous decompression the volume harvested is similar to that reported harvested from the posterior iliac crest for single-level fusion.   © 2011 Elsevier Inc. All rights reserved.

Keywords: Local bone graft; Posterolateral lumbar fusion; Decompression; Iliac crest bone graft; Bone morphogenic protein

Introduction

Local bone graft has long been used in lumbar fusions. The use of local graft harvested from the facets was part of the original description of a posterolateral fusion by Watkins [1,2] in 1953, which was developed for patients with previous wide posterior decompression.

Local bone graft has been recommended to augment or replace iliac crest bone graft (ICBG) in short-segment lumbar fusions [3–8]. Controlled trials have indicated that local graft in some posterior-approach lumbar-fusion techniques may have similar clinical and fusion outcomes as an ICBG method [7,8].

The technique and volume of bone graft potentially harvested in posterior lumbar surgery have not been well defined. Some authors have implied the amount available is clinically unimportant [9–11], whereas others have indicated that it can replace the need for harvesting of bone graft from the ilium [7,8]. Although various local bone graft volumes have been reported from individual series, these reports have not described in detail the technique for harvesting local bone from the various bony elements nor have they described a method for measuring the harvested bone.

In this technical report, we present a method used to harvest local bone during single-level posterolateral lumbar fusion for degenerative conditions. A simple and readily available measuring device is described, and the volume of local bone graft harvested in 25 consecutive patients is reported.

Methods

Consecutive patients undergoing lumbar posterolateral fusion with or without instrumentation for degenerative processes were studied. These patients were seen in a university practice in northern California. Demographic and preoperative clinical data were recorded. Local bone graft was harvested by a standard method in each patient and the volume measured by a standard procedure.

Our practice during the time period of this study was to harvest local bone graft and secondarily harvest ICBG only if the local graft appeared insufficient given the size and quality of the intended graft bed.

Technique

A midline approach was used in each patient. The spine was exposed from the upper tip of the cephalad vertebrae to be fused to the inferior facet of the caudal vertebrae and laterally to the tips of the transverse process.

If clinically indicated, a posterior decompression was performed. A high-speed burr was used for this decompression and later decortication. A standard 60-cc sputum/specimen catch-cup was placed in line with the surgical suction with 1 cc of 1:1000 heparin solution. Through suction of the operative field after burring, the shavings were captured in this container and the uncoagulated blood filtered through a gauze sieve.

The cephalad and caudal spinous processes were amputated, leaving the cephalad half of the cephalad spinous

process intact; if possible, as dictated by the decompression (Fig. 1, Top).

The posterior aspect of the facets to be fused were then resected with a curved osteotomy in the plane of lamina and extended laterally to the posterior surface of the transverse process. In a severely arthritic segment, this usually delivered two to four large pieces of corticocancellous bone. During decompressions, variable amounts of medial facet were also resected using a chisel and mallet and saved (Fig. 1, Middle, Bottom).

These harvested pieces (spinous processes, lamina, posterior and medial portions of facet, as well as osteophytic projections) were then cleaned of all soft tissue and combined with the burr shavings. These were morcelized and measured by gentle packing of the local bone graft into proximal end of a dissembled 50-cc graduated syringe.

Statistical methods

Descriptive statistics were used for demographic and clinical features. Comparative statistics of binomial data was performed using a chi-square test.

Funding

Results

A total of 25 patients were studied (Table). The most common diagnosis was degenerative spondylolisthesis with spinal stenosis (12 patients, 48%). Ten patients (40%) had a previous decompression at the level of fusion. One additional patient had a laminotomy with an X-stop implant at this level, which had eroded the spinous process and displaced. Three of the decompression patients had more than one previous decompression, and these were all recurrent disc herniations. Nine patients had in situ posterolateral fusions and 16 had transpedicular screw and rod constructs for instrumented fusions. Six of these were unilateral constructs. Addition of instrumentation was predicated on the stability after decompression and/or the attempt to correct or prevent a deformity.

The mean volume of local bone graft harvested was measured to be 25 cc. The range was 12 to 36 cc. Local bone graft was augmented by iliac crest bone in six of 25 patients (24%). The distribution of bone graft volumes is given in Fig. 2. Only seven of 25 patients had 20 cc or less of local bone graft available for fusion.

The amount of local bone graft harvested in patients with previous decompressions was slightly less (23.9 cc) than those without (26.0 cc), but this difference was not statistically significant with these small numbers. Similarly,

Fig. 1. Local bone harvesting for a single-level posterolateral fusion. (Top) A lateral view with schematic resection depicted; (Middle, Bottom) Axial views at the disc level and just below with schematic resection depicted.

men had slightly more local bone graft harvested (26.3 cc) compared with women (23.2 cc), but again this was not statistically significant.

Discussion

Local bone graft has been used for many years to augment or replace ICBG in posterior fusions. In the 1950s, Watkins originally described the technique of "posterolateral fusion" of the lumbar spine after previous wide laminectomy. This method included the use of local bone from the facets and other elements to augment autogenous bone rotated down from the iliac crest [1,2]. This original description stresses that preparation of the facet joints for fusion and packing with local bone graft is an integral part of the procedure.

It has been clear that in certain circumstances, local harvested bone graft appeared to work as well as ICBG without the attendant morbidity of harvesting the iliac wing for autogenous bone. Violas et al. [12], again stressing the need of a careful facet preparation and graft impaction, found that local bone was sufficient in adolescent scoliosis surgery. For posterolateral fusion or posterior interbody fusion, it has been shown that local bone graft may be as effective in achieving short-segment lumbar fusion as ICBG with less morbidity [3–8,13].

Several studies have looked at ICBG volumes. Ahlmann et al. [14] reported harvesting an average of 55 cc of iliac crest bone to repair large bone defects associated with osteomyelitis and limb salvage surgery. More commonly for single-segment lumbar fusions, lower volumes of ICBG from as little as 20 cc [7,15] and as much as 35 cc [9,10] have been reported. It has been suggested that lesser amounts of ICBG dissection and harvesting result in lesser postoperative morbidity [15,16].

The volume of local bone graft harvested in short-segment lumbar fusions has not been well described. In a study of Japanese adults having fusion for degenerative lumbar spondylolisthesis, Inage et al. found local bone graft harvesting ranged from a mean of 14 cc for a single-level fusion to 30 cc for a three-level fusion. Using an average of 14 cc of local bone graft, Ohtori [7] found comparable fusion rates to ICBG harvesting.

Compared with the North American patients in this present study, the Japanese cohort for single-level fusions reported by both Inage et al. and Ohtori et al. had less local bone graft harvested (14 cc compared with 25 cc). The method to measure the volume of bone graft was not clear in those studies, and a measurement bias in either study may account for some difference. However, the Japanese cohort was older than our group, and this may result in less bone stock to harvest. Perhaps more importantly, the patterns of spondylosis and degree of osteophytosis may be different in North American and Japanese patients. Finally, the average height and weight of Japanese persons of that

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Table
Clinical and demographic characteristics of 25 patients

Characteristics	n
Total number of patients	25
Age	59.8
Male (%)	13
Smokers, n (%)	4 (52)
Self-described racial/ethnic group	
European	36
African	4
Asian	3
Latin American	3
Pacific Islander	2
None given	2
Weight (kg)	80.9
Worker's compensation	6
Diagnosis	
Degenerative spondylolisthesis	12
Recurrent disc herniation	4
Spinal stenosis	4
Stenosis and herniated disc	3
Degenerative scoliosis/stenosis	2
Previous decompression	11
Iliac crest harvested	8
Posterior instrumentation	16
Local bone graft harvested (cc)	24.9 (12–36)

age is smaller than that for North American patients (10–15%) and likely accounts for a majority of the difference [17,18].

It is difficult in our experience to determine when ''enough'' bone graft has been harvested for any particular fusion. In about 25% of our group, the attending surgeon's impression was that the local bone graft was inadequate and an ICBG was used to augment the fusion. This is a subjective assessment at this point, and an accurate method of assessing adequate bone graft bulk has not been described to date.

Conversely extremely small bone graft volumes may be associated with poor or delayed progression to fusion in the

Fig. 2. Number of patients (y-axis) with each range of local bone graft volume harvested (in cubic centimeters, x-axis).

adult lumbar spine. Cammisa et al. [15] suggested that autogenous bone graft volumes of 10 cc or less were of limited value. Dimar et al. described using as little as 7 cc of ICBG with no local bone in a randomized clinical trial and reported lower fusion rates in this control group. This low graft volume, when coupled with a lack of formal facet fusion in the Dimar et al. [9,11] studies, would be inadequate in our opinion to anticipate a robust fusion mass.

The size and quality of the decorticated bone bed determines how much graft may be required. Obviously, a very tall individual may have as long a grafting bed in a single level as a small individual would for two levels. Similarly, the health and vascularity of the decorticated surface is important. The preparation of the facet joint, as pointed out by other authors, has in our experience been extremely important. The facet should be cleared of soft tissue and articular cartilage and bone graft impacted into the prepared cancellous surface. To allow exposure of the articular surface, we have found that the removal of the posterior facet surface provides both an excellent source of graft material and exposes a large area of cancellous both on either side of the facet.

As stated in our technique, we believe it is important to leave the cephalad edge of the spinous process intact. We try to leave a stout base to the spinous process and preserve the ligaments extending to the next higher segment to preserve stability. Even without removing this structure, we still were able to harvest more than 20 cc of local bone in more than 70% of subjects. In those requiring additional bone graft from the iliac crest, the amount needed was much less, and lower graft volumes have been associated with less postoperative morbidity [16].

Conclusion

Local bone graft harvesting has historically been an integral part of the posterolateral fusion procedure in the lumbar spine. This study demonstrated that by using bone resected during decompression, prominent posterior facet segments and spinous process bone, approximately 25 cc of bone graft can be harvested from a single lumbar level. Even in patients with previous posterior decompression, this is similar to the volume of bone graft usually obtained from the iliac crest for single-segment fusion.

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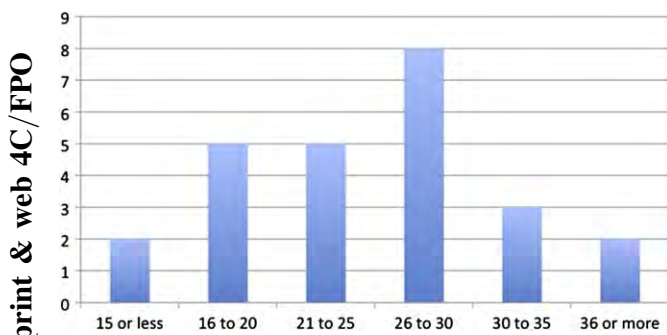
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An injectable method for noninvasive spine fusion

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Abstract

BACKGROUND CONTEXT: Bone morphogenetic proteins (BMPs) induce bone formation but are difficult to localize, and subsequent diffusion from the site of interest and short half-life reduce the efficacy of the protein. Currently, spine fusion requires stripping, decortications of the transverse processes, and an autograft harvest procedure. Even in combination with BMPs, clinical spinal fusion has a high failure rate, presumably because of difficulties in localizing sufficient levels of BMP.

PURPOSE: The goal was to achieve reliable spine fusion through a single injection of a cell-based gene therapy system without the need for any surgical intervention.

STUDY DESIGN: Eighty-seven immunodeficient (n=44) and immune-competent (n=43) mice were injected along the paraspinous musculature to achieve rapid induction of heterotopic ossification (HO) and ultimately spinal arthrodesis.

METHODS: Immunodeficient and immune-competent mice were injected with fibroblasts, transduced with an adenoviral vector to express BMP2, along the paraspinous musculature. Bone formation was evaluated via radiographs, microcomputed tomography, and biomechanical analysis.

RESULTS: ew bridging bone between the vertebrae and the fusion to adjacent skeletal bone was obtained as early as 2 weeks. Reduction in spine flexion-extension also occurred as early as 2 weeks after injection of the gene therapy system, with greater than 90% fusion by 4 weeks in all animals regardless of their genetic background.

CONCLUSIONS: Injection of our cell-based system into the paraspinous musculature induces spinal fusion that is dependent neither on the cell type nor on the immune status. These studies are the first to harness HO in an immune-competent model as a noninvasive injectable system for clinically relevant spinal fusion and may one day impact human spinal arthrodesis.   © 2011 Elsevier Inc. All rights reserved.

Keywords: Gene therapy; Spine fusion; Heterotopic ossification; BMP2; Spinal arthrodesis

Introduction

Of the more than one million bone grafts performed worldwide annually, 50% involve spinal fusions, and of these patients, 25% complain of donor site pain from the autograft harvest for up to 2 years postoperatively [1]. These complications have driven the search for and subsequent use of alternatives. This has led to the growing use of bone morphogenetic proteins (BMPs), which have long been demonstrated to help induce bone formation [2–4].

Recombinant human BMP2 is Food and Drug Administration approved for use on collagen sponges for the treatment of open long bone fractures and in metal cages for spinal fusion. Without the sponge or cage, the BMP2 cannot be localized and tends to diffuse from the desired site, reducing its efficacy and leading to adverse effects, such as edema, ectopic bone formation, and bone resorption in the graft area [5]. Because BMPs are so rapidly diffused, large quantities of the protein are required, making the procedure very expensive [3]. Furthermore, although the use of recombinant human BMP2 for spinal fusion may negate the need for an additional surgical procedure to harvest autograft bone, the method still necessitates an operation that, with the inclusion of the sponge or cage, introduces a permanent foreign object into the body [4]. Posterolateral spinal fusion also requires decortication of the transverse processes of the vertebrae targeted for fusion, stripping of the paraspinous musculature from bone, and a fairly long operative time [1,6]. Beyond the pain associated with decortication and stripping are often other complications. Stripping the musculature compromises the stability afforded by these muscles, disrupts the blood supply to both bone and muscle, and promotes scar formation. In the clinical arena, even with addition of the powerful morphogen BMP2, there is still a considerable clinical failure rate [5], causing researchers to search for better methods to deliver higher doses.

Recently, Shore et al. [7] demonstrated that a mutation in the BMP2 receptor was responsible for the observed heterotopic ossification (HO) in the genetic disease fibrodysplasia ossificans progressiva. Soft tissues in individuals with this genetic disorder are replaced with heterotopic bone. The HO can rapidly form within a few days and even replace skeletal bone if it becomes weight bearing by fusing to existing bone in such a manner that stress shielding initiates resorption. It readily fuses to the skeletal bone and often leads to ankylosis of the joints. Harnessing this capacity in a targeted controlled manner would potentially facilitate regeneration and repair solutions for skeletal bones.

Gene therapy approaches hold much promise in spinal fusion applications by delivering locally high levels of BMP2 to elicit robust targeted HO; however, the efficient transduction of cells poses a problem for many of the currently tested systems and results in low BMP2 expression [8]. In many such spinal fusion studies, this problem is then exacerbated by inclusion of a collagen sponge or other biomaterial that rapidly binds the BMP2, again reducing its effectiveness. For instance, although adenoviral vectors producing BMP2 (AdBMP2) have been used to elicit spinal fusion in rats, the transduced cells were surgically implanted with collagen sponges or demineralized bone matrix after decortication of lumbar transverse processes [9]. Such inclusion of a biomaterial and invasive decortication procedures cause inflammation, which potentially weakens bone healing [5].

Here, we percutaneously deliver cells expressing high levels of BMP2 to launch HO at a targeted location, with the goal of fusing two or more vertebrae within the lumbar spine. We deliver these BMP2-transduced cells without a carrier via injection into the paraspinous musculature. Of the studies using AdBMP2 to elicit spinal fusion in rodents [9–11] (reviewed in Yoon et al. [12]), none have taken into account the fact that without prior manipulation of rodent cells, adenoviral vectors can only minimally elicit bone formation, if at all [13]. We demonstrated this conclusively in previous studies showing that when murine cells were transduced with AdBMP2 at the same multiplicity of infection with and without the aid of a lipid polyamine (GeneJammer; Stratagene, Inc., La Jolla, CA, USA), only those treated with this compound were able to elicit bone formation in vivo. This is because of the fact that the receptors for human adenovirus are present only on human cells. In many murine cell lines, such as NIH3T3, there is no adenovirus receptor at all [14]; therefore, without using special compounds to allow attachment and internalization of the adenovirus, the transduction is exceedingly poor in the rodent cells [15]. As a result, immune-deficient models must be used to achieve the desired bone formation [16]. When using immune-competent animals, lentiviral vectors outperform adenoviral vectors [11] in spite of the fact that the number of genomes that enter the nucleus and produce BMP2 is almost 100 times higher in the latter. In our previous studies, we were the first to demonstrate the ability to harness the production capacity of the adenoviral BMP2 vector in rodents [13,17], and we apply it here in a spinal fusion model. Hence, ours is the first spine fusion model using an adenoviral vector in an immune-competent host that shows the true potential of this powerful vector. In addition, because the virus replicates episomally, meaning that it is not incorporated into the host chromosome nor passed onto daughter cells like lentiviral vectors are, the adenovirus is not perpetuated in vivo and thus has a better safety profile. Adenovirus is also safer than lentiviral vectors because adenoviruses induce a strong immune response and transduced cells are cleared within 4 to 5 days [17]. Because adenoviral vectors are considered safer, it is more likely that of the gene therapy approaches, the ones using adenoviral vectors will make it into the clinical arena. Thus, any adenoviral system capable of eliciting a bone formation response within this 4- to 5-day time frame has a potential clinical impact in humans.

Materials and methods

Cell culture

Human diploid fetal lung fibroblasts (MRC-5) and murine osteoblasts (MC3T3-E1) were obtained from the American Type Culture Collection (Manassas, VA, USA) and propagated in a humidified incubator at 37°C and 5% CO_2 in α-minimum essential medium (Sigma, St. Louis, MO, USA) and Dulbecco's Modified Eagle's Medium (Sigma, St. Louis, MO, USA) supplemented with 10% fetal

bovine serum (HyClone, Logan, UT, USA), 1000 U/L penicillin, 100 mg/L streptomycin, and 0.25 μg/mL amphotericin B (Invitrogen by Life Technologies, Gaithersburg, MD, USA), as previously described [17]. Murine stromal cells (W20-17; a gift from Genetics Institute, Cambridge, MA, USA) were propagated and maintained as described by Thies et al. [18].

Adenoviruses

The construction, propagation, and purification of the adenoviral vectors used in this study were previously described in detail [13,19]. Briefly, replication-defective adenoviruses were constructed with deletions of the E1 and E3 viral genes by in vivo homologous recombination in 293 cells. The vectors used were a first generation human type 5 adenovirus (Ad) constructed to contain complementary DNAs for human BMP2 (AdBMP2) or no transgene (AdEmpty) in the E1 region of the viral genome [19]. During purification, virus particles (VPs) were quantitated by the plaque-forming unit assay, in which each plaque signifies infection of one cell by one virus. For the viruses AdBMP2 and AdEmpty, the VP:plaque-forming unit ratios were 1:83 and 1:111, respectively, and the viruses were confirmed to be negative for replication-competent adenovirus.

Cell transduction

Cells from the murine cell line MC3T3-E1 (1×10^6) were transduced with a BMP2 adenoviral vector or control (AdBMP2 or AdEmpty, respectively) at a viral concentration of 5,000 VP/cell with 1.2% GeneJammer, as previously described [13]. Briefly, GeneJammer was added at 3% to α-minimum essential medium without supplements and incubated for 10 minutes at room temperature. Adenoviral vectors, either AdBMP2 or AdEmpty, were then added at the aforementioned concentrations, and the mixture was further incubated for 10 minutes at room temperature. This virus solution was then diluted with supplemented α-minimum essential medium to achieve 1.2% GeneJammer per volume. The resulting transduction solution was used to coat the MC3T3-E1 monolayer with the minimum volume necessary to wet the cells, which were then incubated in a humidified incubator with 5% CO_2 at 37°C for 4 hours. After 4 hours, the transduction solution was diluted with supplemented medium at an amount appropriate for cell culture and replaced in the incubator overnight.

MRC-5 human fibroblasts (1×10^6) were transduced as previously described with a BMP2 adenoviral vector or control, AdBMP2 or AdEmpty, respectively [19]. Briefly, virus was added at a viral concentration of 2,500 VP/cell to fresh supplemented Dulbecco's Modified Eagle's Medium and incubated with cells in a humidified incubator with 5% CO_2 at 37°C overnight.

BMP2 quantification

Bone morphogenetic protein-2 expression was evaluated for MC3T3 and MRC-5 cells transduced with AdBMP2 or AdEmpty using enzyme-linked immunosorbent assays and alkaline phosphatase assays. Culture supernatant from transduced cells were collected 72 hours after adenovirus transduction and assayed with a BMP2 Quantikine enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, MN, USA) to measure BMP2 expression. Transduced cells were cocultured with W20-17 cells, with the transduced cells in the 0.4-μm pore polycarbonate membrane six-well transwell inserts (Corning Inc., Lowell, MA, USA) and the W20-17 cells in the wells of six-well plates. After 72 hours, W20-17 cells were assayed for alkaline phosphatase activity using a chemiluminescence procedure [20]. Three freeze-thaw cycles were performed in a 100-μM/cm^2 concentration of 25 mM Tris-HCl (pH 8.0) and 0.5% Triton X-100 to extract cellular alkaline phosphatase. This alkaline phosphatase activity was then measured by adding a ready-to-use CSPD (Tropix; Applied Biosystems, Foster City, CA, USA) substrate with Sapphire-II enhancer (Tropix; Applied Biosystems, Foster City, CA, USA) to the samples. After a 2-second delay, the light output from each sample was integrated for 10 seconds with a luminometer (TD-20/20; Turner BioSystems, Sunnyvale, CA, USA). Alkaline phosphatase levels were recorded in relative luminescence units and normalized to protein content with the bicinchoninic acid assay, using bovine serum albumin to derive a standard curve. Bone morphogenetic protein-2 levels and functional activity were found to be similar to previously published results per cell number and virus dose [8].

Spinal fusion

Female nonobese diabetic severe combined immunodeficiency (NOD/SCID; n=44) and C57BL/6 (n=43) mice (8–12 weeks old; Charles River Laboratories, Wilmington, MA, USA) were maintained in accordance to Baylor College of Medicine Institutional Animal Care and Use Committee protocols. Fig. 1 depicts an overall schematic of the process. Each mouse strain was separated into two major groups, animals receiving control-transduced cells or animals receiving BMP2-transduced cells; NOD/SCID animals received AdBMP2- (n=35) or AdEmpty-transduced cells (n=9), whereas C57BL/6 mice received AdBMP2- (n=32) or AdEmpty-transduced cells (n=11). Animals receiving AdBMP2-transduced cells were further divided into groups to be harvested at 2, 4, and 6 weeks (for C57BL/6, n=8, 4, and 20, respectively; for NOD/SCID, n=11, 12, and 12, respectively). All animals receiving AdEmpty-transduced cells were harvested at 6 weeks. Before paraspinous injections, the back of each mouse was prepared and a limited portion of the skin was incised to reveal the paraspinous muscles. Although the injection
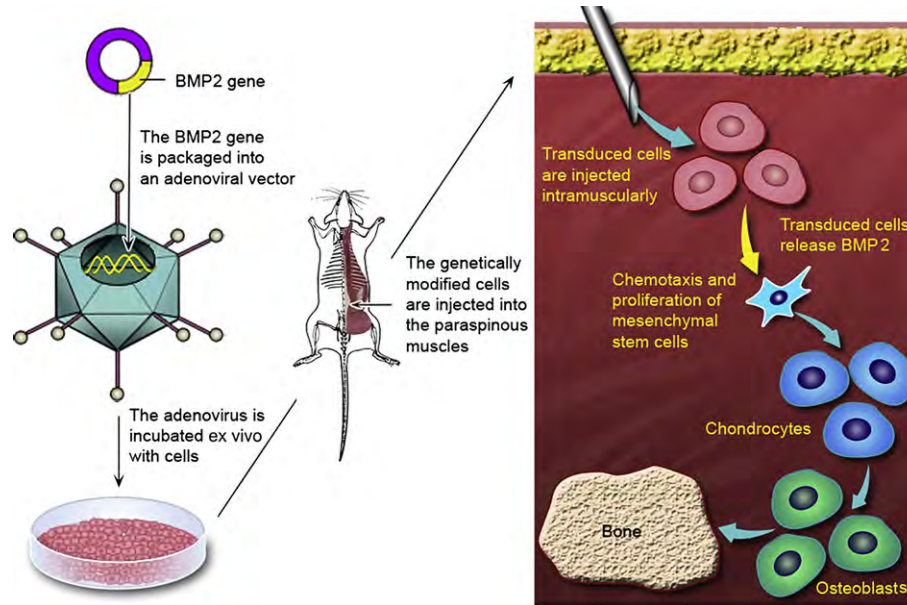
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Fig. 1. Schematic depiction of spine fusion using the cell-based gene therapy system. Adenoviral vectors producing BMP2-transduced cells injected into the muscle rapidly recruit host cells to undergo all stages of endochondral ossification [24,36]. Arrows indicate order of steps. Within 1 week, mineralized osteoid can be detected in photomicrographs and radiographs. BMP2, bone morphogenetic protein-2.

could have been conducted without opening the skin, the incision was performed to ensure appropriate placement of the transduced cells. Transduced cells were collected for injection after removal from tissue culture plates with trypsin and resuspension in phosphate-buffered serum at a concentration of 5×10^6 cells per 100 μL of phosphate-buffered serum and then delivered by intramuscular injection into the right paraspinous muscles along the length of the spine (Fig. 2). The placement of the needle was performed manually. The needle was positioned within the longissimus muscle, 1- to 2-mm distant from the lamina and spinous process. Multiple deliveries of approximately 10 μL of cell suspension were injected at about 2 or 3 mm intervals along the spinal segment targeted by advancing the needle without completely withdrawing it. Cells were not injected with the needle in contact with the bone. A total of 50 μL of volume was injected for each animal. After 2, 4, and 6 weeks, mice were sacrificed, and the spines with attendant musculature were removed and fixed at room temperature overnight in 4% formaldehyde solution (VWR, Sugar Land, TX, USA).

Microcomputed tomography analysis

All harvested intact spines (N=87) were scanned at 14-μm resolution with a commercial microcomputed tomography system (GE Locus SP; GE Healthcare, London, Ontario, Canada). Three-dimensional reconstructions of the spine and any mineralized tissue in the surrounding muscle were created at 29-μm resolution to visualize endochondral mineralized tissues. A volume of interest was defined for each specimen, and a threshold was chosen to exclude any nonmineralized tissue. The total

volume of endochondral bone was then measured (eXplore MicroView, v. 2.0; GE Healthcare, London, Ontario, Canada), and preexisting bone from the spines of the animals was excluded from mineralized tissue measurements.

Biomechanical testing

After microcomputed tomography, formaldehyde-fixed spines from each group (n=64) were encased in alginate to obtain flexion and extension radiographs. Spines with attendant soft tissue from the C57BL/6 mice, AdEmpty (6 weeks, n=8), AdBMP2 (2 weeks, n=8; 4 weeks, n=4; and 6 weeks, n=8), and NOD/SCID mice (n=9, each group) were suspended in an in-house mold. Alginate powder was combined in an equal volume to water (30 mL of each) and mixed until smooth. The alginate was poured into the mold and allowed to solidify such that no portion of the spine protruded from the solidified alginate. Solidified alginate blocks were placed in an in-house spring loaded clamp with rigid 110° arcs (Fig. 3). Radiographs were taken of molds in flexion and extension orientations for each spine. These digitized radiographs were used to quantify intervertebral motion with Food and Drug Administration–approved software (KIMAX QMA; Medical Metrics, Inc., Houston, TX, USA) that has been validated for the clinical assessment of spinal fusion by measuring relative intervertebral motion. The software compares radiographs in extension and flexion, detects the concomitant intervertebral rotation and translation, and has been demonstrated to report the movement with an accuracy better than 0.5° for rotation and 0.5 mm for translation between adjacent vertebrae [21,22]. Intervertebral motion was measured at each vertebral level. Preliminary data [23] demonstrated

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Fig. 2. Delivery of the transduced cells into the paraspinous musculature. The needle was positioned by hand within the longissimus muscle, 1- to 2-mm distant from the lamina and spinous process. Left image shows multiple delivery sites of the transduced cells (AdBMP2 or AdEmpty) of approximately 10 μL of cell suspension per site at 2- to 3-mm intervals along the spinal segment targeted. Multiple delivery is accomplished by advancing the needle without completely withdrawing it. (Right) Cell delivery (a total of 50 μL per animal) was performed with the needle in the muscle, never in contact with the bone. AdBMP2, adenoviral vectors containing complementary DNAs for human bone morphogenetic protein-2; AdEmpty, adenoviral vectors with no transgene.

that the normal mouse spine undergoes an average of 5° of intervertebral motion using this test. Spines were considered fused when adjacent vertebrae did not exhibit rotation beyond 1.5°, which represents a 70% reduction in motion.

Histologic analysis

After biomechanical testing, four fixed spines from each group and time point (n=32) were isolated for histologic analysis as previously described [24] to confirm that any apparent mineralized bone observed on the radiographs was true osteoid and that it had integrated at these tentative points of fusion. The spines and adjacent tissues were decalcified in hydrochloric acid, processed, and embedded into a single paraffin block, where serial sections were then cut at a thickness of 5 μm. Every fifth section was stained with hematoxylin and eosin and observed under light microscopy to identify the tentative points of fusion. Representative photomicrographs (2× and 4×) of samples from each model were taken 2, 4, and 6 weeks after induction of HO. To further confirm the vertebral fusion, a subset of spines (n=9; one from each group and time point, two from NOD/SCID at 6 weeks) were immersed in bleach for approximately 1 hour, which removed all soft tissues. Midway through this process, nylon wire was threaded up the spinal canal to maintain the relative position of the vertebrae.

Statistical analysis

Statistical analysis was performed as described previously [17]. Briefly, all data were taken in triplicate and reported as mean and standard deviation. A Student *t* test with a 95% confidence interval (p<.05) was performed between the control and each experimental condition.

Results

Radiologic analysis of bone formation

In all animals receiving AdBMP2-transduced cells, heterotopic bone formation occurred along the injection site

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Fig. 3. (A) Schematic of the in-house flexion device. After 2, 4, or 6 weeks, spines were harvested with attendant soft tissue attached, (B) encased in a block of alginate, (C) then placed in the device to induce flexion or extension at 110°, and (D and E) radiographed. (D and E) Representative images used to evaluate biomechanical function of spinal fusion. (D) Spine in extension. (E) Spine in flexion. Such images were evaluated with KIMAX QMA software (Medical Metrics, Inc., Houston, TX, USA) to determine whether adjacent vertebrae rotated more than 1.5° (30% of normal).

adjacent to the spine, with greater than 90% of all animal spines showing bridging and fusing to the skeletal bone (Fig. 4F–L) by 4 weeks (NOD/SCID: 89% and C57BL/6 mice: 100%). Two-dimensional microcomputed tomography images show cross sections through the injected area (Fig. 4A–D, M–P). The radiographs and three-dimensional reconstructions demonstrate that both the immune-incompetent system, NOD/SCID mice receiving human cells transduced with AdBMP2 (Fig. 4I–P), and the immune-competent system, C57BL/6 mice receiving AdBMP2-transduced allogeneic murine cells (Fig. 4A–H), appear to produce similar bone within 4 to 6 weeks. In particular, the newly formed heterotopic bone appears to have integrated into the vertebral cortical bone (Fig. 4B–D, O–P). These points of fusion appear to be in the laminae region of the vertebra, with most of the fusions encompassing the entire spinous and transverse processes, suggesting robust significant fusion. This new bone appears to be remodeled with a contiguous cortical bone exterior. Although only 44% of the NOD/SCID spines harvested at 2 weeks were fused by this time point, unfused spines from this group showed potential points of fusion: Fig. 4N shows an early time point in which the heterotopic bone, although extensive, has not yet fused into the vertebrae. Interestingly, we did not see a similar failure to fuse in wild-type mouse models—at all time points, each

animal injected with AdBMP2-transduced cells had developed a fused spine. In other words, in the C57BL/6 mice, the fusion rate was 100%: as seen in Fig. 4B, even at the same early 2-week time point, the substantial bone has fused to the adjacent vertebra. Despite the 100% fusion, there are some areas in the C57BL/6 animals in which not all of the newly formed bone has fused with the spine: in Fig. 4C, some of the heterotopic bone appears to have formed slightly distal to the vertebral bodies. At no time was bone formation observed within the spinal canal. In no cases was bone formation or bridging observed in the spines receiving the AdEmpty-transduced cells.

Biomechanical analysis to confirm reduced motion of the spine

Comparisons of harvested spine radiographs subjected to 110° of flexion and extension revealed reduced intervertebral motion in animals receiving AdBMP2 (Fig. 3D,E). Spines were considered fused when the KIMAX QMA software, which is used to report clinical fusions [21,22], indicated that relative intervertebral rotation between adjacent vertebrae was reduced by 70% of normal (Table). When analyzed for relative intervertebral rotation and translation, in no cases did tissues receiving AdEmpty-transduced cells
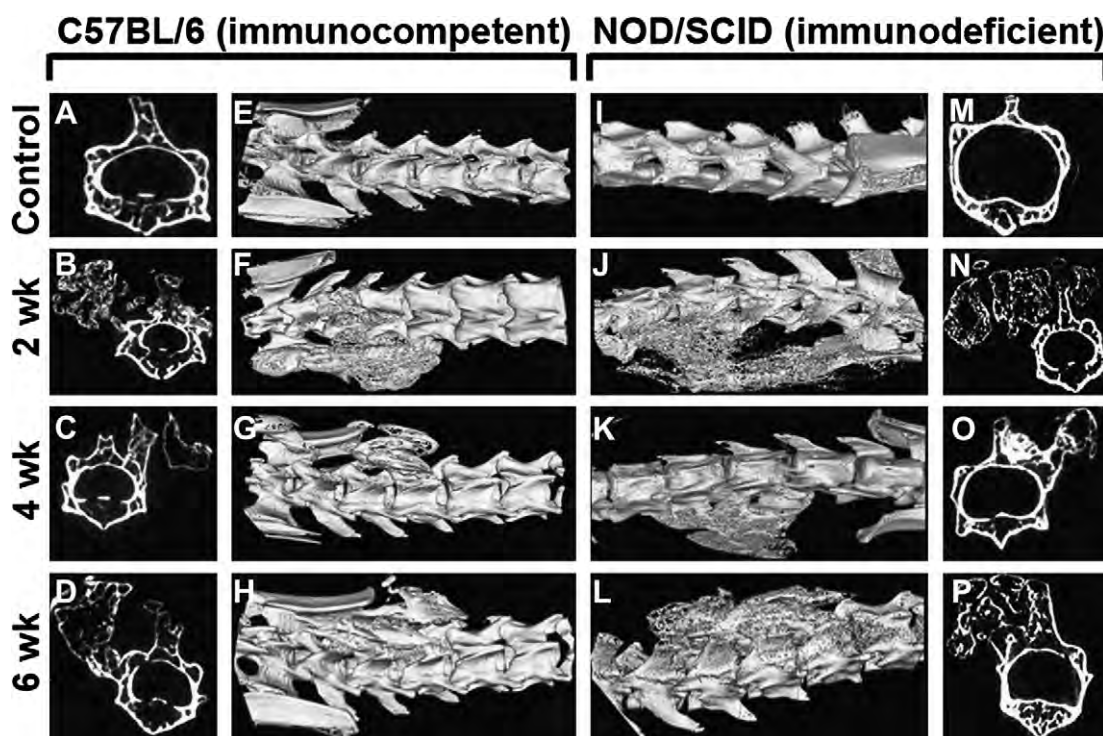
Fig. 4. (A–H) Radiographs at 2, 4, and 6 weeks of C57BL/6 and (I–P) NOD/SCID spines imaged after intramuscular injection into the paraspinous musculature of cells transduced with AdEmpty control virus (A, E, I, and M) or AdBMP2 (B–D, F–H, J–L, and N–P). Control animals injected with AdEmpty were scanned 6 weeks after delivery of the transduced cells (A, E, I, and M). Mice receiving the AdBMP2-transduced cells were scanned 2 weeks (B, F, J, and N), 4 weeks (C, G, K, and O), and 6 weeks (D, H, L, and P) after the initial induction of HO. Two-dimensional X-rays (A–D: C57BL/6, and M–P: NOD/SCID) show a cross section through the three-dimensional reconstructions (E–H: C57BL/6, and I–L: NOD/SCID) of tentative fusions between the HO and the vertebral bone. NOD/SCID, nonobese diabetic severe combined immunodeficiency; HO, heterotopic ossification; AdBMP2, adenoviral vectors containing complementary DNAs for human bone morphogenetic protein-2; AdEmpty, adenoviral vectors with no transgene.

show a reduction in motion or spine stiffening. Conversely, in NOD/SCID animals that received the human cells transduced with AdBMP2, approximately 44% of the spines at 2 weeks and 89% of those at 4 and 6 weeks had reduced movement, consistent with fusion of at least one level. Interestingly, in the C57BL/6 group receiving murine AdBMP2-transduced cells, 100% of the spines at all time points consistently showed a reduction in motion correlating with fusion.

Histologic analysis of the spine fusion

Hematoxylin and eosin–stained slides revealed structures of mature bone in all de novo bone samples from animals receiving BMP2-transduced cells (Fig. 5). Osteoclasts, osteocytes, and tentative bone marrow elements in the heterotopic bone were observed in these slides, as well as cartilage, analogous to the growth plate structures in the normal long bone. The new heterotopic bone appeared to grow in a direction toward the skeletal bone, with the most mature bone being distant from the skeletal bone in the 2-week samples. There is substantial new bone adjacent to and fused with the more mature vertebral bone along the transverse process and laminae region of the vertebra (Fig. 5A and B). Although mature bone with tentative marrow elements was observed at 2 weeks, this structure was always distal to the vertebral bone (data not shown), suggesting that the original HO started de novo in the muscle and grew toward the vertebrae to encompass the existing bone.

At the 4-week time point (Fig. 5C and D), the heterotopic bone displays a much more mature morphology and a cellular process appears to be rapidly removing the mature cortex of the skeletal bone at the point of fusion. This large number of cells involved in this process has resulted in a moth-eaten appearance of the mature cortical bone of the vertebra during its apparent removal and replacement by the maturing heterotopic bone (Fig. 5G).

Table
Spinal fusion in injected animals

Treatment*	N	Immune status†	Time at harvest (wk)	Animals with two or more vertebrae fused (% of group)
AdEmpty-transduced cells	9	Deficient	6	0 (0)
AdBMP2-transduced cells	9	Deficient	2	4 (44)
AdBMP2-transduced cells	9	Deficient	4	8 (89)
AdBMP2-transduced cells	9	Deficient	6	8 (89)
AdEmpty-transduced cells	8	Competent	6	0 (0)
AdBMP2-transduced cells	8	Competent	2	8 (100)
AdBMP2-transduced cells	4	Competent	4	4 (100)
AdBMP2-transduced cells	8	Competent	6	8 (100)

AdBMP2, adenoviral vectors containing complementary DNAs for human bone morphogenetic protein-2; AdEmpty, adenoviral vectors with no transgene.

* Treatment indicates type of cells injected.
† Immune status indicates type of animal used. Immune-deficient animals were nonobese diabetic severe combined immune-deficient mice. Immune-competent animals were C57BL/6 mice.

The origin of the large number of cells is unclear. At the 6-week time point, the cortical boundary is completely remodeled (Fig. 5E and F) with the newly formed and original bone contiguous as one integrated structure with a well-defined cortex and trabecular interior, which houses the bone marrow. At this point, the only evidence distinguishing the newly formed HO is the presence of substantial amounts of adipose tissue, which is found within heterotopic regions in contrast to the mature marrow within the vertebra (Fig. 5F). All cases (Fig. 5) show what appears to be fusion with the transverse process within the laminae region of the vertebra, which was the target region for fusion. Depending on the depth of the histology section, more or less of this region was involved in the fusion site. In many cases, the fusion actually encompassed both the spinous process through the laminae to the transverse process. In all tissues analyzed, the HO appeared to grow into the vertebral body, which itself did not appear to undergo growth, and there was no evidence of new bone formation within the spinal canal, similar to radiologic findings.

Functional demonstration of fusion

The nine spines with soft tissues bleached away confirmed fusion in all specimens displaying biomechanical constraint during mechanical testing. A representative 6-week spine shows that five vertebrae of the lumbar spine are remodeled into a single structure (Fig. 6, Top). In cases that did not meet our biomechanical criteria for fusion (several NOD/SCID animals at 2 weeks) in that intervertebral motion did not appear to be constrained after induction of bone formation, there was heterotopic bone that was not integrated with the vertebrae but rather formed individual bones, confirming our biomechanical findings.

Soft tissue removal and induced scoliosis demonstrate the fusion of the spine (Fig. 6, Top, Bottom Right). Representative radiographs show a distinct curvature of the spine toward the area of new bone formation and tentative fusion in animals receiving AdBMP2-transduced cells (Fig. 6, Bottom Right). This scoliosis has occurred in 6-month-old growing mice in both immune-competent and incompetent strains. This was observed in a large number of animals with heterotopic bone and tentative fusion but absent in animals that received the control cells (Fig. 6, Bottom Left).

Discussion

To determine if our cell-based gene therapy system induces spine fusion through intramuscular injection without invasive surgery or additional carriers, we established two different murine models for testing. We previously characterized these models and found the HO in the mouse quadriceps muscle to be similar [17]. In this study, we applied this cell-based gene therapy system to the paraspinous musculature in the region of the vertebral laminae to determine whether heterotopic bone formation could be

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Fig. 5. Hematoxylin and eosin–stained representative photomicrographs of tentative vertebral fusion with the heterotopic bone, taken 2 (A, B: 2× and 4×, respectively), 4 (C, D: 2× and 4×, respectively), and 6 weeks (E, F: 2× and 4×, respectively) after initial injection of the AdBMP2-transduced cells. (E) A representative photomicrograph (10×) of a sample taken 4 weeks after the initial injection of AdBMP2-transduced cells. As can be seen in this sample, there are a significant number of cells associated with the boundary between the new heterotopic and the old vertebral bone (arrows). Scale bars are 2.0 mm except for G, which is 300 μm. AdBMP2, adenoviral vectors containing complementary DNAs for human bone morphogenetic protein-2.

targeted to this location; form bridging bone between two or more skeletal vertebrae; and ultimately fuse the spine. In this approach, either AdBMP2-transduced cells or AdEmpty-transduced cells are delivered to the paraspinous musculature of a mouse through a simple injection at points adjacent to the levels of desired fusion. With this system, HO is generated rapidly, fused, and remodeled into two or more of the adjacent vertebrae, reducing spine motion. The fusion appeared to be rapid, at a time scale of 2 weeks, and the new bone was limited in size and scale to regions of muscle that received the cells.

Fusion of both the heterotopic bone to the skeletal bone and the resultant bridging of two vertebrae were rapidly achieved through simple injection. Within 2 weeks, 44% to 100% of the spines in the two different murine models were considered fused by all criteria—radiologic, histologic, and biomechanical. In samples tested 4 to 6 weeks after induction, greater than 90% of all mice had achieved spine fusion in the two models and noticeable scoliosis was observed radiologically in the animals' spines, suggesting that the fusion could restrain the spine, even during continued growth. Our system is the first approach

We have, however, shown repeatedly that stem cells are not necessary, and that any cell that produces a high level of BMP2 will suffice [8,13,17]. This enables us to qualify cells for our purposes and use them without concern about their stem cell nature. The use of BMP2-producing MSCs also raises questions as to their ultimate fate because they are not destined for immune destruction like our virally transduced cells. In an attempt to avoid the use of such transduced MSCs, Sheyn et al. [26] used transfection techniques to incorporate the BMP6 gene for spinal fusion in immune-deficient mice. This approach failed to achieve complete success because of their admittedly low efficiency of transduction of the ovine cells. We have also found that injection of BMP2-producing cells ultimately induces the production of BMP6 (on Day 2) and BMP7 (on Days 5 and 6) as assessed by microarray analysis (Davis et al., 2007, unpublished). Therefore, it is probably not necessary, and may in fact be detrimental, to use different types of BMPs because administration may not occur at the proper time nor place.

Reported time scales for achieving spinal fusion in various animal models using ex vivo gene therapy approaches, in which virally transduced cells are injected, range between 6 weeks and 3 months; using in vivo gene therapy approaches, in which the virus itself is injected, spinal fusion typically proceeds between 4 and 12 weeks [2,29]. Nevertheless, despite the reported successes using these approaches, such results were tempered with difficulties in isolating stem cell populations to use as delivery cells and problems with low–gene transduction efficiencies [2,29,30]. The work presented here circumvents these issues. Surprisingly, we observed 100% fusion in the immune-competent wild-type mice within 2 weeks of induction, yet only 44% fusion at 2 weeks in the immune-deficient mice. This difference in success rate may be attributable to a learning curve as the small scale of the mouse spine made injections more difficult. On analysis of the three-dimensional reconstructions, it appeared that some of the new bone was slightly distal to the vertebra in the NOD/SCID immune-incompetent mice that failed to fuse, whereas it was more closely associated with the vertebra in the wild type. Previous comparisons of our immunocompetent and immunodeficient models show that they function almost identically in production of heterotopic bone [1]. Therefore, it is unlikely that this difference is linked to the immunodeficiency, but rather that as we progressed, we improved our ability to place the cells proximal to the vertebra within the paraspinous musculature, indicating that placement may be critical to the eventual fusion.

These results suggest that heterotopic bone can be rapidly induced by delivering locally high levels of BMP2. This is not surprising because recombinant BMP2 is currently used clinically; however, the rapid 2-week time frame has not previously been reported (see Mussano et al. [4] for review). This may be a direct result of our

Fig. 6. (Top) Spine fusion was observed in bones isolated from the mouse after induction of targeted heterotopic ossification. Associated soft tissues were removed by bleaching, leaving only the bone. A wire was threaded through the spinal column, to preserve the orientation of the vertebra. Unfused vertebrae hang free; fused vertebrae remain joined and rigid. Ruler is in millimeters. Radiographs of mouse spines at 6 weeks after induction of spine fusion AdEmpty- (Bottom Left) or AdBMP2-transduced (Bottom Right) cells. (Bottom Right) The image shows obvious curvature of the spine suggesting a significant scoliosis, as compared with the normal mouse spine, shown in Bottom Left. AdBMP2, adenoviral vectors containing complementary DNAs for human bone morphogenetic protein-2; AdEmpty, adenoviral vectors with no transgene.

reported in the literature to achieve clinically relevant spinal fusion in an animal model within 2 weeks through a single intramuscular injection. Although it can be argued that several other systems achieve this goal in various animal models [25–28], each of these studies fall short of a clinically relevant regimen. In a study by Hasharoni et al. [25], the authors inject recombinant human BMP2–producing mesenchymal stem cells (MSCs) into the paraspinous muscles of immune-deficient mice. Although this is indeed a percutaneous approach, it is not a clinically relevant percutaneous approach in that this study neither reports the percentage of mice that achieve fusion nor performs biomechanical testing of the fusion. In addition, the assumption is that MSCs are required in addition to their production of BMP2.

ability to produce high levels of BMP2 for a prolonged period of time. This process may be explained by taking cues again from the human genetic disease fibrodysplasia ossificans progressiva, in which HO can readily occur within 1 week; this disease is caused by a mutation in a BMP receptor that leads to constitutive activity but can still be further activated through addition of BMP [31]. Thus, physiological doses of BMP2 normally released after trauma effectively become high doses, leading to rapid HO at the local injury site. During adenovirus transduction, multiple VPs enter the cell with large amounts of vector DNA effectively delivered to the nucleus. Because of its episomal (extrachromosomal) nature, the vector DNA is present at high numbers, driving high-level expression of BMP2.

Therefore, one of the things separating adenovirus from other gene therapy vectors is the high level of transgene expression that can be achieved after efficient transduction. As long as the virus can efficiently infect the specific cell types [13], this system can be used to produce these high doses of BMP. Thus, we have developed this as a cell-based gene therapy system rather than a direct approach, to circumvent potential problems with inefficient uptake of the adenovirus, problems that prohibit production of the BMP2 levels necessary for achieving rapid fusion [8]. This is perhaps why our approach is so extremely effective at making rapid targeted bone. Furthermore, by prior transduction of the cells with the virus, no free adenovirus is delivered to the animal, minimizing adverse effects of the virus on other tissues.

In addition to forming bone rapidly, this study is the first to demonstrate the ability of HO to form clinically relevant bridging bone and fuse adjacent vertebral bone without contribution from the skeletal bones. Both current clinical approaches using recombinant BMP2 and other gene therapy approaches [1] require exposure of the vertebra and decortication to induce bone growth and ultimately fusion of the skeletal bone to heterotopic bone. Often, autologous bone graft is harvested to use in place of ectopic bone, which requires an additional extensive surgical procedure. Here, through both histologic analysis and biomechanical analysis, we demonstrate the ability of the heterotopic bone to fuse into skeletal bone without prior exposure and decortication.

Furthermore, all spines receiving the AdBMP2-transduced cells appeared to have extensive heterotopic bone formation on radiologic analysis. In no cases did we observe any ossification in the spinal canal. In the animals receiving AdEmpty-transduced cells, there was no ossification whatsoever. The results suggest that the heterotopic bone formation is targetable to a discrete location. On radiologic analysis of samples taken 2, 4, and 6 weeks after initial injection of the AdBMP2-transduced cells, heterotopic bone was found between the transverse process adjacent to the paraspinous musculature receiving the cells and laminae. This heterotopic bone eventually encompassed these structures, fusing the spine. In many cases, we observed significant fusion of the entire laminae, from the tip of the spinous process through the entire transverse process. There was some variation in the amount of vertebral bone involved in each fusion, but this did not seem to affect the overall arthrodesis itself. Furthermore, because the transduced cells can target the location of bone formation, perhaps the variation observed could also be a result of placement of these cells within the spinous musculature of the mice. Regions of soft tissue adjacent to corresponding distal structures of the same vertebra were not involved in any bone formation and appeared normal in these radiographs.

Histologic analysis of this model suggests that the heterotopic bone grows into the skeletal bone with a somewhat organized growth plate, cortex, and tentative periosteum, similar to the vertebral bone. Initially less mature bone is observed at the junction of fusion, and depending on the model, this results in a reduction of motion by 2 weeks in approximately 44% to 90% of the animals tested. As the two bones fuse, there appears to be a cellular reaction, which is destructive to the vertebral cortex. This process allows for the replacement of the cortical boundary with mature trabecular bone and bone marrow over time. It is not surprising from these results that in all cases, the latter 4- and 6-week structures are well fused both histologically and biomechanically. Interesting to note, by 6 weeks, the old vertebral structure is gone with the only remnants of the newer heterotopic bone found in the marrow cavity. This observation suggests that adipose may form in the bone marrow cavity before the housing of true bone marrow because in all less mature heterotopic bone, we observed extensive white fat, whereas in the vertebral bone marrow, there was very little if any present. Whether this tissue plays a key role in establishment of the marrow is yet to be determined.

Ideally, on successful fusion, the newly fused heterotopic bone should restrict mobility within the spine. Therefore, biomechanical testing was performed to measure the changes in angle of the spine under force. In spines with a significant reduction in mobility, we observed well-integrated collagen fibers running contiguously through the bone, suggesting that it was a remodeled single structure, whereas those that appear as two separate structures under polarized light were not capable of reducing flexion-extension. In animals with reduced spinal mobility, we also observed scoliosis because of the arthrodesis. Because the epiphyseal growth plates of rodents do not close until 2 years of age (the approximate life span of laboratory mice), their skeletons essentially do not stop growing [32]. The fusion of the vertebrae in essence mechanically fixed the right side of the spine, causing imbalanced growth, resulting in scoliosis. The ability to fuse the spine without surgical intervention would be a significant advancement in health care. The creation of a bony fusion by means of the percutaneous injection of a biologically active material, without extensive surgical dissection and -bony decortication, would have many clear clinical advantages. This system is quite versatile, in that any cell can be used as a delivery cell, as long as adequate transduction with adenovirus is achieved [33]. Thus qualified cell lines used in

current clinical trials, such as MSCs, can be readily adapted for use in this cell-based gene therapy system, making it very feasible to introduce clinically. The rapid onset of bone in addition to the rapid clearance of the transduced cells bode well for the future therapeutic application of this system in humans. The goal of this work was to demonstrate that these gene therapy methods can be used to rapidly and reliably accomplish fusions without extensive and highly invasive surgical procedures. The location of the fusions that we demonstrate here is equivalent to the classic posterior approach to spinal fusion. Although this location for the fusion bone has ample human precedent clinically, the technique could be reasonably applied to fusions in other anatomic areas, for example, the posterolateral (intertransverse process) location. Alternate locations like the intertransverse process were not pursued in this study because getting the transduced cells to this target in these very small animals is challenging without X-ray guidance.

In this study, the fusion mass was large and induced scoliosis because of our delivery of cells only into the right paraspinous muscles. For clinical applications in humans, we envision that delivery would be balanced on both sides of the spine and BMP2 expression would be controlled by a ''TET-on'' (tetracycline-on) or other inducible system in which gene expression is controlled by the administration of tetracycline or other small molecule [34]. In such a system, the size of the fusion mass could be monitored, and over time, this fusion would be remodeled: we have seen remodeling of the fusion mass in the animals (and indeed in humans). We expect that the ultimate dimensions and stiffness of the fusion mass will have more to do with Wolff's law than the dimensions of the original fusion.

The system presented herein could potentially markedly decrease the pain, blood loss, and recovery time for patients undergoing these procedures, thus significantly reducing health care and associated costs. Our viral vectors have already been used clinically in Phase I-II cancer trials to augment the expression and immunogenicity of the antigen latent membrane protein-2 and have resulted in complete tumor response of patients with relapsed lymphoma [35]. With the safety of the viral vector already established in humans, using the vector to deliver BMP2 clinically is an attainable goal. This system could potentially improve success rates of spinal fusion, thus improving the quality of health care in this arena overall. With large animal studies and clinical trials yet to be performed, such a future is a ways off, but our system is the first step toward that day.

Acknowledgments

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Commentary

Commentary: Gene therapy for spinal fusion

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COMMENTARY ON: Olabisi RM, Lazard ZW, Heggeness MH, et al. An injectable method for noninvasive spine fusion. Spine J 2011;11:545–56 (*in this issue*).

Gene therapy is a potential method to deliver growth factors to the human spine with the intent that this intervention will lead to consistent and reliable bone formation, resulting in a successful spinal fusion. As spinal fusion surgery is a commonly performed procedure, strategies have been developed to maximize fusion rates and hopefully clinical success rates and obviate the need for the harvest of autogenous bone graft from the iliac crest. Although historically autogenous bone graft has been used for spinal fusion, the morbidity of the graft harvest has been an issue, particularly for long fusion or massive defects [1,2].

With the identification of the bone morphogenetic proteins (BMPs) by Urist in the 1960s, the use of these growth factors has been refined, resulting in recombinant forms of BMP-2 and BMP-7 being available for clinical use. Gene transfer is a highly effective method of delivery of these growth factors, and there have been multiple animal studies on this topic showing very high success rates for spinal fusion in these animal models [3,4]. Gene therapy using adenoviral vectors specifically for BMP-2 (adBMP-2) have been widely studied with high reported success rates. The first rodent intertransverse process fusion model using adBMP-2 in an ex vivo methodology was published in 2003, demonstrating extremely high fusion rates with abundant bone formation that was superior to comparable doses of recombinant human BMP (rhBMP)-2 [5]. Bone marrow cells were transfected with the adenoviral vector coding for BMP-2, and these cells were implanted into a rodent spinal fusion model. Subsequent studies showed high promise using gene transfer with a variety of cellular delivery vehicles and other types of vectors, all with high radiographic success rates.

With the availability of rhBMP-2 for use in humans, the interest in gene therapy as a delivery mechanism waned. This was primarily because of the ease of use of the recombinant form of the protein and the widespread availability without the need for cells, transfection times, or the risks of viral proteins, leading to an inflammatory response. This coupled with the fact that the ex vivo method of gene therapy appeared to be a time-consuming and complicated process to the average surgeon required special abilities of cell culture and gene transfer techniques. Other concerns were for the potential for contamination, need for the proper timing of cell harvest and transfection, and dosage

issues that were not defined, all combining to make the process quite daunting and difficult to implement [6,7]. When compared with the ease of use of opening a bottle of rhBMP-2 and reconstituting it within minutes and allowing the use during the time of the actual surgery without preplanning, gene therapy appeared much less attractive.

As the rhBMPs were used clinically in humans, off-label use became popular, and it was used throughout the spine for cervical, thoracic, and lumbar fusions. As off-label use became more widespread, significant complications were documented that appeared to be because of an intense local inflammatory reaction and overabundance of bone formation in certain situations. Concerns for patient safety led to a 2008 Public Health Notification by the Food and Drug Administration issued to health-care professionals to notify them of the potential life-threatening complications that may occur when rhBMP is used in cervical spine fusion procedures. The problems with the recombinant BMPs led us to reexamine other delivery methods that may be more successful with potentially lower complication rates. This has generated recent renewed interest in gene therapy.

Clearly, the use of gene transfer techniques has significant hurdles with regard to human trials, the potential for reactions to the potential viral proteins that may be introduced along with the treatments, and dosage and delivery refinements to secure the correct amounts of growth factors appropriate for the clinical situation [8–10]. The Food and Drug Administration approval barriers are enormous, with the fact that very few human gene therapy trials have been approved. The specific advantages of gene therapy need to be maximized and effectively demonstrated to justify its use in nonlethal pathologies such as those in most spinal fusion patients, especially when there are readily available alternatives that do not carry these potentially negative attributes [11].

Olabisi et al. [12], in this issue of *The Spine Journal*, appear to capitalize on the advantages of gene therapy over recombinant proteins, which could justify further study, and, if successful, advancement into human trials [13,14]. Gene transfer techniques may efficiently deliver a large volume of growth factors over a sustained period of time. This may result in greater bone formation and higher healing potential. In an open surgery or a minimally invasive surgery, alternative bone graft options would arguably suffice. Olabisi et al. [12] used a noninvasive fusion model in which none of the currently available bone grafting options or recombinant growth factors would typically heal the spine. The percutaneous injection of the transfected cells resulted in a noninvasive fusion that could clinically translate into a spinal fusion in a human subject by a simple series of injections via a percutaneous needle. This would represent a significant advantage over any currently available options and would transform modern spinal fusion surgery. Ideally, this would result in advances in patient comfort, rehabilitation, and recovery time. At the same time, this technique could potentially decrease the morbidity of an open surgery along with the associated surgical complications, operative time, cost, risk of general anesthesia, blood loss, pain, and logically a reduction in overall cost, provided the injection was not overwhelmingly expensive. Eliminating the risk to the patient of the open surgery and medical comorbidities would theoretically lead to safer surgeries.

The authors used their method of short transfection times with a fibroblast cell line instead of a typical stem cell–like deliver vehicle, which I believe would be more compatible with ease of use and potentially less theoretical complications from cell transformation. It also appears that the transfection process and delivered cells did not elicit a clinically significant inflammatory response that inhibited bone formation, as the immune-competent animals healed at a similar rate as the immune-deficient animals. This may signify a more biologically compatible process; however, larger animal models and ultimately human trails would be needed to test this theory.

The results of this study appear to put forth the advantages of gene therapy, resulting in a percutaneous spinal fusion with an injection of cells transfected with an adenoviral vector coding for the gene for BMP-2. The methodology used by the authors, as reported, also appears free of many of the past problems with gene therapy techniques without a significant inflammatory response. It is important to realize, however, that little or no complications in early testing were also reported with the first direct uses of rhBMP in humans, but these became a serious problem with wider application and observation. Nonetheless, I do think that this is an outstanding study. Clearly, further testing and refinement are necessary to define the appropriate dosage in regard to the number of cells and potential complications. I also believe that it is quite possible that as the authors move into larger animal models, we may be able to define more of the problems that are associated with these techniques, but the initial data are encouraging. I do congratulate the authors on their study.

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Basic Science

Biomimetic calcium phosphate coatings as bone morphogenetic protein delivery systems in spinal fusion

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Abstract

BACKGROUND CONTEXT: Use of recombinant human bone morphogenetic protein-2 (rhBMP-2) has been shown to enhance spinal fusion rates. Case reports of soft-tissue swelling, ectopic bone formation, and osteolysis have recently surfaced. It is hypothesized that incorporation of rhBMP-2 within a calcium phosphate (CaP) coating may help to localize delivery and mitigate these complications.

PURPOSE: To compare the characteristics of posterolateral fusion between rabbits receiving rhBMP-2 delivered via physical adsorption to a collagen sponge or rhBMP-2 incorporated within the physical structure of a CaP coating on a collagen sponge.

STUDY DESIGN/SETTING: New Zealand white rabbit model of posterolateral lumbar fusion at L5–L6.

METHODS: Eighteen (18) New Zealand white rabbits underwent posterolateral spinal fusion at L5–L6. Rabbits received bilateral collagen sponges that were either coated with CaP (n=3), coated with CaP and dipped in rhBMP-2 (n=3), coated with a hybrid CaP–rhBMP-2 film (n=6), or coated with a hybrid CaP-rhBMP-2 film and dipped in rhBMP-2 (n=6). Animals were followed weekly with radiographs and were sacrificed at 6 weeks. Fusion masses were further characterized by manual palpation, computed tomography, and histology.

RESULTS: Radiographic evaluation showed that animals in Group 3 (incorporated BMP) fused at 4 weeks, whereas animals in Group 2 (adsorbed BMP) and Group 4 (incorporated and adsorbed BMP) fused by 6 weeks. Animals that received rhBMP-2 physically adsorbed to the collagen sponge showed extension of the fusion mass beyond the L5–L6 level in 56% of cases and bone resorption in 78%. Histology of fusion masses showed mature bone formation in animals belonging to Groups 2, 3, and 4 and extensive osteoclast recruitment in animals belonging to Groups 2 and 4.

CONCLUSIONS: Delivery of rhBMP-2 via incorporation within CaP coatings results in increased rates of radiographic fusion. The burst release profile of rhBMP-2 adsorbed to surfaces, although effective in achieving fusion, may result in increased osteoclast recruitment. © 2011 Elsevier Inc. All rights reserved.

Keywords: rhBMP-2; Bone graft substitute; Drug delivery; Animal model; Calcium phosphate

Introduction

Autogenous bone graft (autograft) harvested from the iliac crest is considered the gold standard in achieving successful arthrodesis of the lumbar spine [1]. The harvest of iliac crest bone graft is associated with a clinically significant rate of donor site morbidity and postoperative complications, including persistent pain, numbness, fracture, and herniation of abdominal contents [2]. Pseudarthrosis may

occur despite the use of autogenous bone graft and instrumentation [3–6].

In response to the shortcomings of autograft and allograft usage, numerous alternatives have been investigated. In 1965, Dr Marshall Urist [7] discovered that proteins extracted from bone could induce ectopic bone formation. The purification of the proteins involved in the bone formation process leads to the identification of the biomolecules known as bone morphogenetic proteins (BMPs). To date, of the more than 20 BMPs isolated and identified, BMP-2, BMP-4, BMP-6, BMP-7, and BMP-9 have been shown to possess the greatest osteoinductivity [1].

Because of its highly osteogenic properties, BMP-2 was investigated for use in spinal fusion procedures. Currently, recombinant human bone morphogenetic protein-2 (rhBMP-2; INFUSE Bone Graft; Medtronic Sofamor Danek, Minneapolis, MN, USA) has received approval from the Food and Drug Administration for use in anterior interbody fusion of the lumbar spine [8]. The INFUSE system is also being investigated as an alternative to iliac crest bone graft in posterolateral lumbar fusion [9,10].

Although the osteoinductive capacity of rhBMP-2 is not in doubt, clinical use of the drug bound to Type I collagen sponges has been associated with postoperative complications. Smucker et al. [11] reported increased neck swelling when using rhBMP-2 in the off-label setting of anterior cervical arthrodesis. When using rhBMP-2 in transforaminal lumbar interbody fusion (TLIF), 69% (22 of 32) of levels examined exhibited osteolytic changes in the vertebral body, which were consistent with osteoclastic bone resorption [12]. Joseph and Rampersaud [13] used computed tomography (CT) to prospectively analyze the incidence of heterotopic bone formation in minimal access posterior lumbar interbody fusion and TLIF procedures. The group found a 20.8% rate of heterotopic ossification, with most of the ossification taking place in the foramen, and one case of bone formation in the canal. Although heterotopic ossification did not correlate with poorer outcomes in this series, cases of neurologic impairment from ectopic bone have been reported with off-label use of BMP-2 in posterior lumbar interbody fusion/TLIF [14].

BMP must be delivered to the fusion site by means of a carrier material. Although not yet thoroughly studied, reported complications may be related to the delivery mode of rhBMP-2. Currently, the standard practice involves the physical adsorption of aqueous rhBMP-2 applied to an absorbable collagen sponge immediately before implantation [9,10]. To control bone formation and potentially reduce complications, modifications in the BMP carrier have been investigated [15]. In addition, carrier modifications have been shown to enhance the delivery of rhBMP-2 in nonhuman primate models of posterolateral fusion [16].

Liu et al. [17] used a rat ectopic model to compare rhBMP-2 that was physically adsorbed onto collagen sponges and rhBMP-2 biomimetically (ie, similar to physiological processes) incorporated within a calcium phosphate (CaP) coating on titanium discs. Both physically adsorbed and biomimetically incorporated rhBMP-2 successfully induced ectopic bone formation. However, a greater volume of new bone was formed in the group that received titanium discs coated with rhBMP-2–containing CaP.

Recently, a method to biomimetically deposit CaP coatings on various substrata was developed and can be similarly adapted to deliver BMP in a sustained localized fashion [18–20]. This also involves the incorporation of BMP within the physical structure of a CaP coating, which can be biomimetically deposited on implant surfaces. In this study, the orthotopic application of biomimetic CaP coatings as BMP carriers was investigated using an established rabbit intertransverse fusion model [21,22]. We hypothesized that BMP delivered via a biomimetic CaP coating results in equal fusion rates compared with the current best practice (BMP via physical absorption), while demonstrating more localized and sustained delivery in vivo.

Materials and methods

Graft material preparation

Type I bovine collagen sponges reinforced with hydroxyapatite particles (Healos; Depuy Spine, Raynham, MA, USA) were used as the graft material for the posterolateral lumbar fusion procedure. Healos sponges in each treatment group were cut into strips with dimensions of $50 \times 10 \times 5$ mm (2.5 cc per sponge). Recombinant human bone morphogenetic protein 2 was purchased from R&D Systems (Minneapolis, MN, USA).

Group 1—Biomimetic CaP

The first treatment group consisted of Healos strips with a biomimetic CaP coating. The biomimetic coating process has been described in detail elsewhere [18–20]. Briefly, the Healos strips were immersed in a saturated $CaOH_2$ solution for 20 minutes to encourage ion exchange, which later promotes CaP deposition. Strips were then transferred to vials containing a supersaturated CaP solution (SCPS). The SCPS consisted of a 5.6-mM solution of calcium chloride, a 3.34-mM solution of sodium dihydrogen phosphate, and tris-hydroxymethylaminomethane to buffer to physiological levels. Healos strips remained in the SCPS for 72 hours and the solution was refreshed every 24 hours. After immersion, the strips were allowed to air dry for 12 hours.

Group 2—Biomimetic CaP and adsorbed rhBMP-2

The second treatment group consisted of CaP-coated Healos strips with a physically adsorbed rhBMP-2 film, which was used to simulate the current best practice of soaking a collagen sponge in rhBMP-2 before implantation. The biomimetic CaP coatings were deposited using the method described in the Group 1—Biomimetic CaP section. Fifteen minutes before implantation, 0.8 mL of an aqueous solution of rhBMP-2 (1.2 mg/mL) was dripped

onto the CaP-coated Healos strips using a 1.5-mL syringe to yield a total dosage of 1.0 mg of rhBMP-2 per strip (1.0 mg per side, 2.0 mg rhBMP-2 per animal).

Group 3—Hybrid CaP+rhBMP-2 coating

The third treatment group consisted of a hybrid CaP+rhBMP-2 coating biomimetically deposited on the Healos strips. Hybrid coatings were deposited on the Healos strips by first immersing the strips in a saturated $CaOH_2$ solution for 20 minutes. The strips were then removed from the $CaOH_2$ solution and placed in vials containing SCPS and 0.28 mL of an aqueous rhBMP-2 solution (1.2 mg/mL). Strips remained in the mixture for 72 hours and the rhBMP-2 and SCPS were refreshed every 24 hours. A linear accumulation of rhBMP-2 within the coating was assumed, such that the daily addition of 0.28 mL of the aqueous rhBMP-2 solution would yield strips each with 1.0 mg of rhBMP-2 incorporated.

Group 4—Hybrid CaP+rhBMP-2 coating and adsorbed rhBMP-2

The final treatment group was implemented to determine the benefit of adding a physically adsorbed rhBMP-2 film to a hybrid CaP+rhBMP-2 coating. Hybrid coatings were deposited in a similar fashion to those in Group 3. However, in an attempt to keep the rhBMP-2 dosage consistent among Groups 2, 3, and 4, only 0.21 mL of the aqueous rhBMP-2 solution was added to the SCPS daily. Fifteen minutes before implantation, 0.21 mL of the aqueous rhBMP-2 solution was dripped onto the CaP-coated Healos strips using a 1.5-mL syringe to yield a final dosage of 1.0 mg of rhBMP-2 per strip. Based on the assumption of linear accumulation, 0.75 mg of rhBMP-2 would be incorporated into the coating, whereas 0.25 mg of rhBMP-2 would be physically adsorbed immediately before implantation.

rhBMP-2 incorporation efficiency

Although the target dosage of rhBMP-2 was 1.0 mg for Healos strips in Groups 2, 3, and 4, a biochemical analysis was performed to determine the actual incorporation efficiency of the biomimetic technique. An enzyme-linked immunosorbent assay (rhBMP-2 ELISA, Quantikine; R&D Systems Inc., Minneapolis, MN, USA) was used to determine the amount of rhBMP-2 incorporated within the Healos strips in treatment Groups 3 and 4. Three Healos strips from Groups 3 and 4 were dissolved in 2 M hydrochloric acid to facilitate analysis. The solutions that the strips from Groups 3 and 4 were immersed in were also analyzed by ELISA for the amount of rhBMP-2 remaining, which is an indirect measure of the rhBMP-2 incorporated within the sponge.

Animal model of posterior lumbar fusion

All procedures were performed in accordance with the Institutional Animal Care and Use Committee. Eighteen New Zealand white rabbits (17 females, 3.0–3.6 kg; 1 male, 3.9 kg) underwent anesthetic induction via an intramuscular injection of ketamine hydrochloride/xylazine (35 mg/kg+5 mg/kg, 0.6 mL/kg body weight). A prophylactic dose of enrofloxacin was administered parenterally (10 mg/kg) just before surgery. The rabbits were intubated after anesthetic induction. Anesthesia was maintained via inhaled administration of isoflurane. A posterior approach to the lumbar spine was made using a standard midline incision on the dorsum over L5–L6 [21]. The transverse processes of L5 and L6 were decorticated with a high-speed burr to yield a bleeding bone surface. One Healos strip per side was placed in contact with the transverse processes, while bridging the intertransverse process space of L5–L6. Both collagen strips placed per animal were of the same treatment group. Fascia was closed using vicryl suture and skin was closed with staples.

Animals were extubated on recovery from anesthesia and transferred to cages where they were allowed ad libitum activity. Postoperative analgesia consisted of a fentanyl patch (Duragesic, 25 mcg/hr; Ortho-McNeill-Janssen Pharmaceuticals Inc., Titusville, NJ, USA) and intramuscular buprenorphine (0.03 mg/kg). All rabbits tolerated the procedure well, with the exception of one animal that expired preoperatively because of anesthetic complications. Rabbits underwent fluoroscopic evaluation of the fusion site on a weekly basis. The degree of fusion was assessed by two orthopedic surgeons, blinded to the study, using the key shown in the Table. To facilitate positioning for fluoroscopy, rabbits were mildly sedated with inhaled isoflurane under acute observation. Rabbits were closely monitored during anesthetic recovery. At 6 weeks, the rabbits were sacrificed by an overdose of sodium pentobarbitol. Death was assured via bilateral pneumothoraces. After sacrifice, lumbar spines were imaged fluoroscopically and excised en bloc.

Manual palpation

The degree of fusion was assessed using the manual palpation technique, described elsewhere [21]. Two orthopedic spine surgeons blinded to the treatment groups independently assessed for the presence of fusion (fused or not fused). Specimens without palpable motion between L5 and L6 were considered to be fused. After manual palpation, the spines were immersed in a 10% buffered formalin solution for 1 week before any further analyses.

Table
Radiographic assessment key

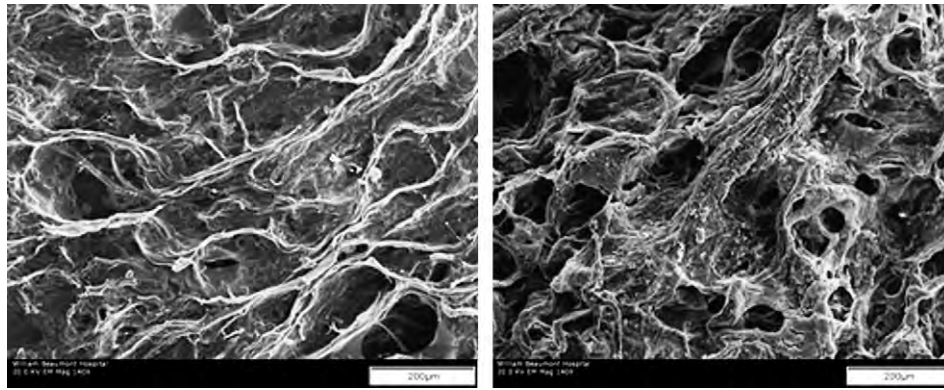| Grade	Description
0	No visible bone formation
1	Bone formation on vertebral bodies, or on transverse processes. Less than 50% of intertransverse process distance bridged
2	Bone formation between TPs which covers greater than 50% of inter-TP gap
3	Continuous bone formation between TPs

TPs, transverse processes.

Fig. 1. Scanning electron microscopy micrographs of (Left) uncoated Healos and (Right) Healos with a hybrid calcium phosphate+recombinant human bone morphogenetic protein-2 film.

Computed tomography

Harvested spines were imaged by CT. Three-dimensional reconstructions of the CT slices were performed. The reconstructed images were analyzed by the blinded observers noted in manual palpation section described above. The volume of new bone in the fusion mass was measured from greater than 0.5-mm–thick axial slices using radiographic analysis software (Vitrea; Vital Images Inc., Minnetonka, MN, USA). New bone volumes were compared between the different groups of animals using analysis of variance with a Bonferroni correction and an $\alpha=0.05$.

Histological analysis

After CT of the harvested spines, the formalin-soaked spines were subjected to histological analysis. The spines were sectioned with a diamond saw to isolate the fused level. The isolated L5–L6 level was then sectioned in the sagittal plane to yield two pieces. Each piece was then placed in an embedding cassette, dehydrated with an ethanol and xylene series, and decalcified. Decalcified specimens were then embedded in paraffin and microtomed into 5-micron thick sections. The sections were rehydrated, transferred to glass slides, and stained with hematoxylin and eosin. Five slides were taken from each side of the L5–L6 segment, for a total of 10 slides per animal. Slides were qualitatively analyzed by light microscopy for new bone formation, bone resorption, and inflammatory response.

Results

Coating structure and rhBMP-2 incorporation efficiency

A uniform, nanostructured CaP film was formed on the surfaces of Healos collagen sponges using the biomimetic technique. The CaP coating was found on all exposed surfaces of the highly porous Healos collagen sponges, as shown in Fig. 1.

Biochemical analysis of the CaP+rhBMP-2–coated Healos sponges was unsuccessful. The concentrated acid solution used to dissolve the coated sponges interfered with

the binding of antibodies and the expression of the color reagent. However, ELISA testing performed on the solutions that the sponges were immersed in revealed that less than 5.6% ($\pm0.8\%$) of the rhBMP-2 remained in the solutions. This measurement indicates that roughly 94% of the rhBMP-2 added to the immersion solutions was incorporated within the CaP-coated Healos sponges.

Incorporation of rhBMP-2 did not affect the formation of the coating at the sponge surface or within pores. The presence of rhBMP-2 was associated with a slight change in coating morphology. Coatings with incorporated rhBMP-2 showed a wavy appearance, with less-defined CaP clusters, as compared with the pure CaP films.

Radiographic evaluation

Evaluation of fluoroscopic images by the blinded observers showed increased levels of bone formation in Groups 2, 3, and 4, as compared with the control group (Group 1). Vigorous bone formation was noted in Groups 2, 3, and 4 as early as 2 postoperative weeks. Observers noted radiographic evidence of solid fusion in animals from Group 3 at 5 postoperative weeks, as shown in Fig. 2. Despite early differences in the radiographic appearance of the fusion mass, animals from Groups 2, 3, and 4 showed similar levels of fusion at harvest. Interobserver agreement on the radiographic assessment of fusion was 96%.
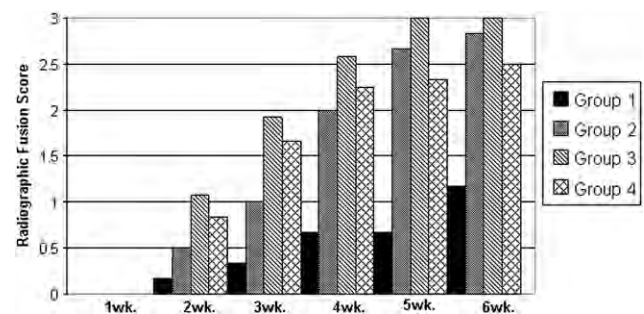

Fig. 2. Radiographic fusion scores for each treatment group as a function of postoperative time.
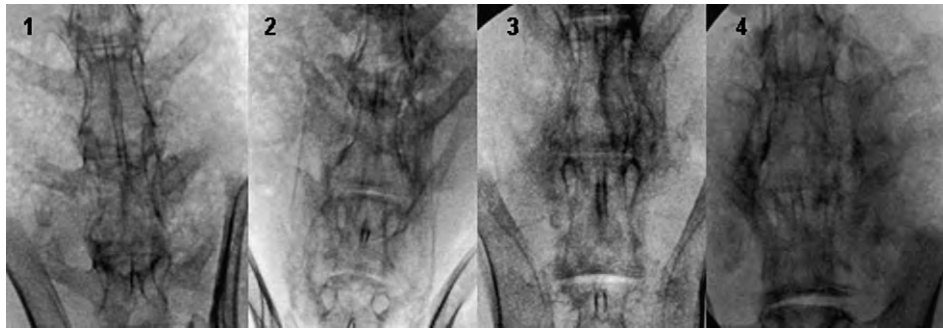
Fig. 3. (Left to Right) Fluoroscopic images of harvested lumbar spines showing the degree of fusion at 6 weeks exhibited by representative specimens from Groups 1 to 4.

Fluoroscopy of rabbit spines at 6 weeks showed differences in the extent and dimensions of fusion masses between the groups. Animals that received only a CaP-coated Healos sponge without rhBMP-2 (Group 1) showed thickening of the transverse processes and some dimensional changes to the vertebral bodies. None of the Group 1 animals exhibited a continuous bridge of bone across the intertransverse space. Robust fusion masses were noted for animals in Groups 2, 3, and 4 at the time of euthanasia. Fusion masses from Group 3 animals were confined to one level, whereas the fusion masses from Group 2 and 4 animals often extended beyond the intended level of fusion, as shown in Fig. 3.

Computed tomography

Three-dimensionally reconstructed CT scans aided in the evaluation of fusion masses from harvested rabbit spines. Analysis of the 3-dimensional reconstructions confirmed many of the observations made during assessment of fluoroscopic images. Transverse processes and vertebral bodies were markedly thickened in Group 1 animals, while little to no bridging bone was present. The fusion masses in all Group 3 animals remained localized to the intended fusion site, whereas fusion masses in Group 2 and 4 animals often extended beyond the L5–L6 level, as shown in Fig. 4. Two of the three animals in Group 2 and three of six animals in Group 4 showed fusion of an adjacent level. One animal from Group 2 and one animal from Group 4 showed fusion masses extending beyond the levels immediately adjacent to the intended site of fusion (L5–L6).

New bone volumes measured from axial CT images showed that animals in Group 2 (11.13 ± 0.81 cm^3) and 4 (9.18 ± 3.47 cm^3) had the highest new bone formation at sacrifice. Animals from Group 3 had new bone volumes averaging 7.77 ± 1.20 cm^3. Significantly less new bone volume (1.08 ± 0.17 cm^3) was noted for Group 1 animals. The difference in bone volume between animals receiving rhBMP-2 (Groups 2, 3, and 4) and those that did not receive rhBMP-2 was statistically significant ($p<.001$, $p=.005$, and
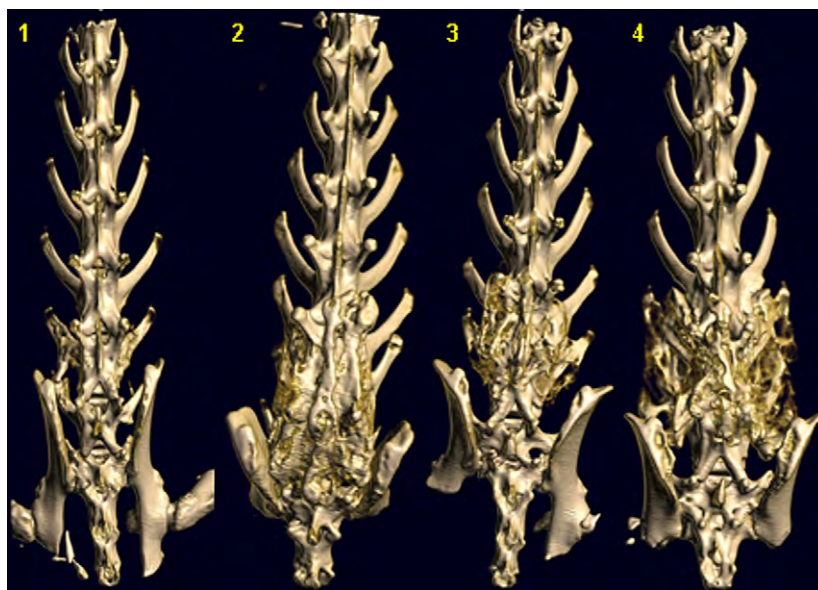

Fig. 4. (Left to Right) Three-dimensional reconstruction images of computed tomography scans performed on representative spines from treatment Groups 1 to 4.

p<.001, respectively). The difference in bone volume was not statistically significant when comparing Group 2 and 3 animals (p=.298), Group 3 and 4 animals (p=.997), or Group 2 and 4 animals (p=.991).

In addition to differences in the relative size of the fusion masses and new bone volumes, 3-dimensional CT reconstructions of spines from Group 2 (3 of 3) and 4 (4 of 6) animals show evidence of bony resorption of the fusion mass. Resorption was not observed in the 3-dimensional reconstruction of any spines from rabbits in Groups 1 and 3.

Manual palpation

Assessment of fusion by manual palpation of harvested rabbit spines showed solid fusion in all animals in Groups 2, 3, and 4. Gross intrasegmental motion in flexion-extension, lateral bending, and axial rotation was noted for all animals in Group 1, indicative of nonfusion.

Histology

Histological analysis of lumbar spines from rabbits in Group 1 showed mature bone formation, characterized by a cortical shell surrounding the fusion mass, on the transverse processes. Some new bone formation was noted on the L5 and L6 vertebral bodies. One animal from Group 1 showed evidence of diffuse trabeculae in the intertransverse process space. Histological sections from rabbits in Groups 2, 3, and 4 all showed mature bone formation on the transverse processes, on the L5 and L6 vertebral bodies and in the intertransverse process space. Areas of new bone formation within the intertransverse process space were also noted for all animals in Groups 2, 3, and 4. Sections from animals in Groups 2 and 4 showed a higher number of osteoclasts per high-power field, as compared with sections from Group 3 animals. Foreign body reactions were found to be most prevalent in histological sections taken from Group 2 animals (Fig. 5).

Discussion

The osteoinductive capabilities of rhBMP-2 have been harnessed for spinal fusion procedures. Currently, rhBMP-2 delivered with an absorbable collagen sponge (INFUSE) is Food and Drug Administration approved for lumbar interbody fusion through an anterior approach [8]. This procedure involves the physical adsorption of aqueous rhBMP-2 applied to the sponge before implantation. However, rhBMP-2 delivered in this format has been associated with complications, specifically with the off-label application in anterior cervical surgery and minimally invasive lumbar interbody fusions [10–14]. In this study, we compared rhBMP-2 delivered via physical absorption on a CaP-coated collagen sponge (Group 2—adsorbed BMP) to a hybrid BMP-2+CaP coating on a collagen sponge (Group 3—incorporated BMP) in an established rabbit intertransverse process lumbar fusion model.

The hybrid CaP+rhBMP-2 biomimetically coated implants (Group 3—incorporated BMP) demonstrated solid intertransverse fusion at 6 weeks as determined by radiograph, manual palpation, CT, and histology. Radiographic analysis demonstrated vigorous bone formation as early as 2 weeks

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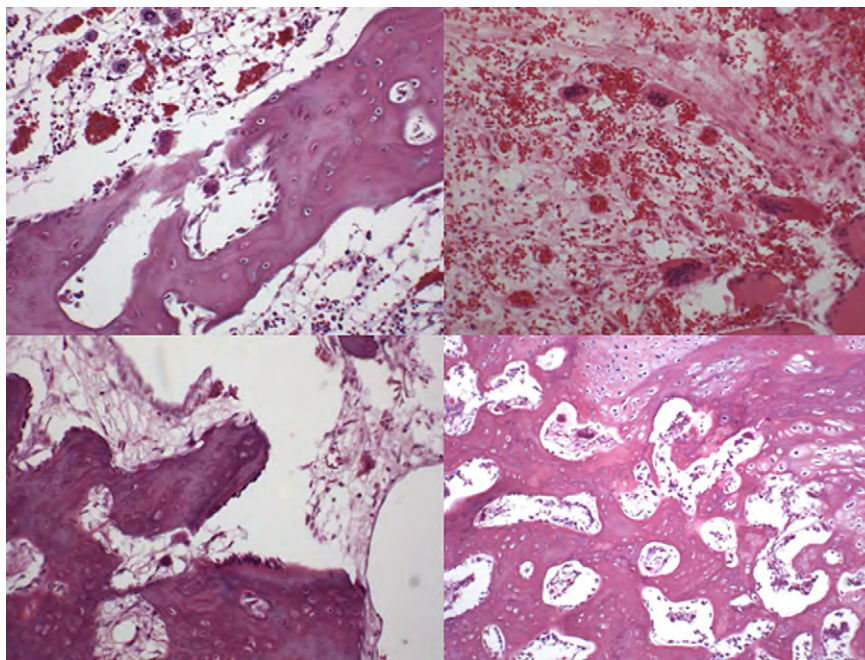Fig. 5. Histological sections from representative animals. (Top left) Limited bone formation and some osteoclastic activity in a Group 1 animal. (Top right) Bone formation, fibroblastic tissue, and foreign body reaction in a Group 2 animal. (Bottom left) Extensive bone formation and limited osteoclast activity in a Group 3 animal. (Bottom right) Extensive bone formation and osteoclastic activity in a Group 4 animal.

in all groups using rhBMP-2 (Groups 2,3, and 4). In the rabbits treated with CaP coating alone (Group 1—no BMP) there was evidence of noncontiguous bone formation only (not solid fusion, see Fig. 3). Furthermore, the addition of physically adsorbed rhBMP-2 to the hybrid CaP+BMP coating (Group 4—incorporated and adsorbed BMP) did not provide any additional benefit over physical adsorption.

The dose of rhBMP-2 used in this study is slightly higher than previous studies using the rabbit posterolateral fusion model. Singh et al. [22] demonstrated that 0.85 mg/side of rhBMP-2 was sufficient to overcome the inhibitory action of doxurubicin. With a similar animal model, Suh et al. [23] used 0.86 mg/side of actually incorporated rhBMP-2. All treatment groups in this study received a target dose of 1.0 mg/side of rhBMP-2. As determined by ELISA, the biomimetic coating process was able to incorporate 94% of the target amount, indicating that the rhBMP-2 dosage (1.0 mg/side) was similar between Groups 2, 3, and 4.

In ectopic animal models, rhBMP-2 delivered via adsorption to preformed inorganic layers results in a rapid initial diffusion of the morphogen on exposure to the physiological environment [17]. To overcome this diffusion, some investigators have used larger concentrations of BMP to achieve successful osteoinduction [24]. Clinically, higher release of BMP into surrounding locations may play a role in complications after off-label utilization. For this reason, an effective carrier that provides more sustained and localized delivery would be advantageous. In this study, the hybrid CaP+rhBMP-2 treatment achieved fusion using a localized and sustained delivery of the osteoinductive agent, as demonstrated by more focused fusion masses with minimal extension beyond a single level This was assessed via radiographic analysis, manual palpation, and quantitative CT analysis. Akamaru et al. [16] also reported that carrier modifications enhanced the delivery of rhBMP-2 in a nonhuman primate model of posterolateral spine fusion. As BMPs are more widely used, the perioperative cost of this technology has been investigated [25]. Enhancing BMP carriers may have cost benefits as well, although specific cost analysis was outside the scope of this study.

Moreover, rhBMP-2 is not only inductive of osteoblastic differentiation but osteoclastic differentiation as well. Studies have suggested that the amount of osteoclastogenesis may have a dose-response relationship to the amount of rhBMP-2 released to the surrounding tissues [26–28]. Joseph and Rampersaud [13] reported CT evidence of bony resorption in 22 of 32 patients after TLIF with BMP-2. Interestingly, the histological evaluation used in this study demonstrated increased numbers of active osteoclasts in the groups using physical absorption (Group 2—adsorbed BMP and Group 4—incorporated and adsorbed BMP, see Fig. 4). Characterization of osteoclastic response was not an initial goal of our study, which limited our ability to provide quantitative data on this finding. Given the elevated rhBMP-2 dosage used in this study and the dose-dependent osteoclastic response to rhBMP-2, the absence of fusion mass

resorption and minimal osteoclast presence in animals that received rhBMP-2 incorporated into a coating (Group 3—incorporated BMP) was a compelling observation. Despite the lack of quantitative data, our findings raise the possibility that carrier modifications may reduce the risk of osteoclast-mediated bone resorption associated with rhBMP-2 usage.

There are several potential limitations to this study. This is an animal study whose findings cannot yet be extrapolated to human clinical applications. Previous animal models have demonstrated that greater amounts of BMP and carrier modifications are required to induce fusion in nonhuman primates [23,28]. However we used a well-established posterolateral spinal fusion rabbit model as a preliminary in vivo analysis. Our findings justify future studies involving biomimetic hybrid CaP+rhBMP-2 coatings in fusions with higher phylogenic species.

In addition, autogenous bone graft remains the gold standard to which bone graft substitutes are compared. The purpose of this study was to investigate whether biomimetic CaP+rhBMP-2 coatings can result in successful fusion from sustained, localized delivery of BMP. We have demonstrated that it results in equally vigorous fusion masses to physically adsorbed BMP (the current standard of application). We did not include an autologous iliac crest bone graft group in our study because of resource limitations.

In conclusion, biomimetic CaP coatings as BMP delivery systems resulted in successful spinal arthrodesis. Our findings suggest that this occurs via a sustained, localized release of BMP into the fusion site. This carrier system modification may potentially enhance efficiency and decrease complications. Future studies will determine the ideal formulation of the coating, elucidating the minimum threshold of BMP to achieve fusion.

Acknowledgments

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Basic Science

Bone morphogenetic protein–binding peptide reduces the inflammatory response to recombinant human bone morphogenetic protein-2 and recombinant human bone morphogenetic protein-7 in a rodent model of soft-tissue inflammation

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Abstract

BACKGROUND CONTEXT: Bone morphogenetic protein (BMP)-2 and BMP-7 are used to enhance bone formation in spine surgery, but the use of these materials is associated with side effects including inflammation, especially in the soft tissues of the neck. Bone morphogenetic protein–binding peptide (BBP) binds BMP-2 and BMP-7 and imparts a "slow-release" property to collagen carrier.

PURPOSE: To test the hypothesis that the addition of BBP will reduce the soft-tissue inflammation induced by the implantation of BMP-2 and BMP-7 on a collagen sponge.

STUDY DESIGN/SETTING: Prospective in vivo rodent model of inflammation.

METHODS: We implanted six different materials absorbed onto collagen sponges: absorbable collagen sponge (ACS) alone; BBP alone; recombinant human bone morphogenetic protein (rhBMP)-2 alone; rhBMP-2 plus BBP; rhBMP-7 alone; and rhBMP-7 plus BBP. Sponges were implanted bilaterally (subcutaneously [SC] and intramuscularly [IM]) into the backs of rats. Using magnetic resonance imaging, inflammation was assessed in terms of soft-tissue edema volume at

3 hours and at 2, 4, and 7 days. The animal subjects were killed on Day 7, and the dimensions of the inflammatory mass were measured manually in the case of SC tissue and those of the inflammatory zone were determined subsequently by microscopic examination in the case of muscle.

RESULTS: Both the SC and the IM soft-tissue edema volumes in the rhBMP-2 plus BBP and the rhBMP-7 plus BBP groups were significantly lower than those observed in the rhBMP-2 alone and rhBMP-7 alone groups. The edema volume associated with BBP alone was greater than that associated with ACS alone but less than that associated with the other treatment groups. The measurements of inflammatory masses and zone yielded similar results.

CONCLUSIONS: Bone morphogenetic protein–binding peptide may reduce the inflammatory response associated with the use of rhBMP-2 and rhBMP-7 in a rodent model of inflammation and in a form that has previously been shown to enhance the activity of BMPs. These preliminary studies suggest that BBP may have the potential to be used in the future to improve healing and reduce soft-tissue swelling in surgical applications of BMPs. © 2011 Elsevier Inc. All rights reserved.

Introduction

Since the approval by the US Food and Drug Administration in 2002 of recombinant human bone morphogenetic protein (rhBMP)-2 for anterior lumbar interbody fusion and rhBMP-7 for revision posterolateral fusion, industry-sponsored trials have reported favorable outcomes related to the osteoinductive capacity of these materials [1,2]. Furthermore, some surgeons have reported that both rhBMP-2 and rhBMP-7 appear to be safe, provided they are used appropriately and placed accurately [3,4]; others have reported serious adverse events including osteolysis, inflammatory cyst formation, implant subsidence, and so forth [5–8]. Furthermore, theoretical safety issues such as antibody formation and dural ossification have been considered. Based on early industry-sponsored safety profile reports and the reported superior osteoinductive capacity, these materials have been used in off-label clinical situations in lumbar to cervical surgical procedures. However, there are numerous reports of significant potential complications, especially when used in the cervical spine, which are concerning [9–11]. Because of the potential for these complications, the US Food and Drug Administration issued a warning in July 2008 of the potentially life-threatening complications of rhBMP-2 and rhBMP-7 when used off-label, especially in the cervical spine.

These concerns and other published reports of soft-tissue swelling after the use of these BMPs lead us to develop a model to study these effects and possibly gain an understanding of the inflammatory response incited by these growth factors. We have developed a rodent model of inflammation to measure the soft-tissue swelling (edema) induced by rhBMP-2 and rhBMP-7 [12,13]. Using this model we have suggested that there is a dose-dependent inflammatory response to rhBMP-2 and rhBMP-7, which peaks between 3 hours and the second postoperative day [12,13].

Bone morphogenetic protein–binding peptide (BBP) is a synthetic cyclic 19 amino acid peptide that binds rhBMP-2 [14] and rhBMP-7 [15]. This peptide has been shown to accelerate and enhance BMP-2–induced osteogenesis in the rodent hindquarter bone formation model [14] and the rodent spine fusion model [16] as well as BMP-7 (osteogenic protein-1)-induced osteogenesis in the rodent spinal fusion model [15]. The presumed mechanism of action for BBP is a "slow release" of rhBMP-2 or rhBMP-7. Support for this contention was observed in in vivo residence time experiments [15].

The purpose of this study was to test the hypothesis that the addition of BBP will reduce the magnitude of inflammation induced by BMPs implanted on a collagen sponge by controlling the rate at which the BMPs diffuse from the implantation site.

Materials and methods

Materials

Experimental materials were obtained from the following sources: rhBMP-2 (INFUSE; Medtronic Sofamor Danek, Memphis, TN, USA); rhBMP-7 (R&D Systems, Minneapolis, MN, USA); BBP (GeneMed, South San Francisco, CA, USA); and absorbable collagen sponge (ACS) (Helistat; Integra Life Sciences Corporation, Plainsboro, NJ, USA).

Experimental design

The experimental doses of rhBMP-2, rhBMP-7, and BBP that were used in this study were based on our observations pertaining to the induction of inflammation by BMPs [12,13] and published studies of the rodent model of spinal fusion [16,17]. Briefly, the dose of BMP that was used was determined by using a simple proportion of the mass of growth factor to body weight of the subject. A small kit of INFUSE used in spine fusion contains 4.2 mg/2.8 mL of rhBMP-2. Assuming a mean weight for a human subject of 70 kg, the delivered dose would be the equivalent of 8.56 mg/100 g. The mean weight of animal subjects used in this study was 249.3 g. The

proportional dose was 21.3 mg. This led to the use of 20 mg of rhBMP-2 as the experimental dose.

A total of six treatment groups were included in this study. Each group contained five animal subjects. Treatment groups differed only by the materials added to the ACSs that were implanted. The treatment groups were ACS (15×5×5 mm) alone, 500 µg BBP, 20 µg rhBMP-2, 20 µg rhBMP-2 plus 500 µg BBP, 20 µg rhBMP-7, and 20 µg rhBMP-7 plus 500 µg BBP.

Surgical procedure

This study used only protocols approved by our institution's Animal Research Committee. Thirty 8-week-old male Lewis rats (weight 211–261 g, mean 249.3 g) were used this study. The animals were anesthetized and then maintained using isoflurane (2–2.5%) in oxygen delivered via facemask. The surgical site was shaved and prepared with alternating betadine and 70% alcohol scrubs. Bland ophthalmic ointment was applied to the eyes to prevent corneal dehydration. Aseptic technique was used for all surgical procedures. The iliac crest was used as the landmark for determining the level of the skin incision. A 25-mm posterior longitudinal incision was made bilaterally 10-mm from the midline.

Subcutaneous implantation

After meticulous dissection, avoiding bleeding in the subcutaneous (SC) space and using complete hemostasis, six different implants were placed directly over the SC fascia on the left side.

Intramuscular implantation

A longitudinal dorsolumbar muscle splitting approach was used. The depth and length of the incision were kept below 10 mm. After meticulous dissection, avoiding bleeding in the SC space and with complete hemostasis, six different implants were placed into the muscle. The fascia was closed using absorbable sutures, whereas a nonabsorbable monofilament suture was used to close the skin incisions. Postoperatively, the animals were allowed to eat and drink ad libitum, and their health status was monitored on a daily basis.

Magnetic resonance imaging evaluation

Soft-tissue edema volume was measured as an index of inflammation after the implantation of experimental materials using a 7-T small animal magnetic resonance imaging (MRI; Bruker Biospin Co., Fremont, CA, USA).

Scans were performed at 3 hours and at 2, 4, and 7 days after surgery for each animal subject. Anesthesia was induced in a purpose-built chamber with 2.5% isoflurane vaporized in oxygen flowing at 2 L/min. Once eye blink and pedal withdrawal reflexes were absent, the animal was placed prone in a custom-built cradle. The animal was monitored for respiration rate while in the magnet. Body temperature was controlled with warm air forced through the magnet bore from an air blower. Axial images with a distance of 2 mm between slices were collected. The volume of the inflammatory (soft-tissue edema) area in the MR images was measured using MIPAV Software (Medical Image Processing, Analysis, and Visualization, Version 4-1-3; NIH, Bethesda, MD, USA) [18,19]. Measurements were made of the edema volume surrounding the SC and intramuscular (IM) implants.

Gross morphology and histological evaluation

After the rats were sacrificed on postsurgery Day 7, the gross morphology of the implantation site was examined. The areas of SC implants were photographed using a digital camera (Samsung 8 megapixels; Samsung, Seoul, Korea). A granuloma-like mass formed in all the rats. The size of this mass was measured in three dimensions (depth×width×height). Inflammation at the IM implantation sites was measured using histological examination. The soft tissue including muscle and the implants were collected and fixed in 10% formalin. Specimens were dehydrated, embedded in paraffin, sectioned (5-µm thickness), and stained with hematoxylin and eosin using standard procedures. Sections were analyzed by using a quantitative scoring method based on the measurement of the actual area of the inflammatory zone surrounding the implants using a Wholeslide Scanner (Aperio XT System, Vista, CA, USA) and the image analysis software (ImageScope, Vista, CA, USA) supplied by the manufacturer (Fig. 1).

Statistical analysis

Two independent measurements were made of the MRI-based gross specimen and histological samples by two observers. The first value provided by each observer was used as a representative value. The reliability of the measured values was examined by evaluating the intraobserver and interobserver agreement using kappa statistics. The mean κ values for the intraobserver and interobserver reliability were 0.82 and 0.78, respectively. Differences between means were tested using Student t test and using SPSS (version 12; SPSS, Chicago, IL, USA). Statistical significance was defined as $p < .05$.

Funding source

Results

Measurement of soft-tissue edema using MRI and MIPAV software

All MR images showed a high signal intensity because of the inflammatory response induced by the experimental materials. The intensity of the responses to the different materials is illustrated graphically in Fig. 2.

The data pertaining to the calculated volumes of the inflammatory responses to the different implanted materials

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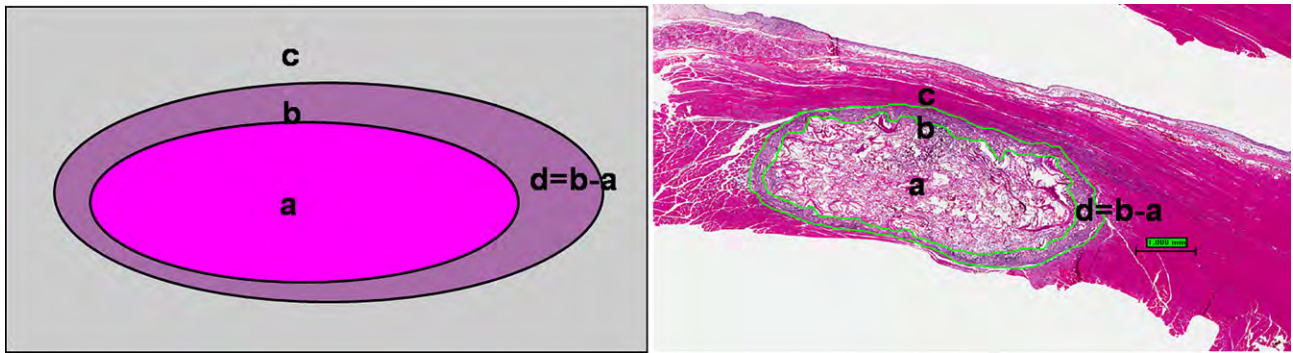
Fig. 1. Quantitative scoring method based on the measurement of the actual area of the inflammatory zone. a indicates the implanted material (absorbable collagen sponge±bone morphogenetic protein) zone; b including a indicates the inflammatory zone; c indicates surrounding muscle fiber zone; and d indicates the actual area of the inflammatory zone (b−a).

are shown in Table 1. The corresponding statistical analysis is shown in Table 2. At all time points, the soft-tissue edema volume of the BBP alone treatment group was significantly higher than that of the ACS alone group but significantly lower than those of either the rhBMP-2 alone group or the rhBMP-7 alone group (Figs. 2 and 3A–D, Tables 1 and 2). With respect to the IM implants, the BMP-2 plus BBP group was statistically lower than the BMP-2 alone group at all time points (Fig. 3A, Tables 1 and 2). The BMP-7 plus BBP group was lower than the BMP-7 alone group at all points, but statistical significance was not reached at 3 hours and at 7 days (Fig. 3C, Tables 1 and 2). With respect to the SC implants, the inflammatory edema volume induced by the BMP-2 plus BBP group was significantly lower than that of the BMP-2 alone group at all time points (Fig. 3B, Tables 1 and 2). The inflammatory edema volume in the BMP-7 plus BBP group was lower than that of the BMP-7 alone group at all time points,
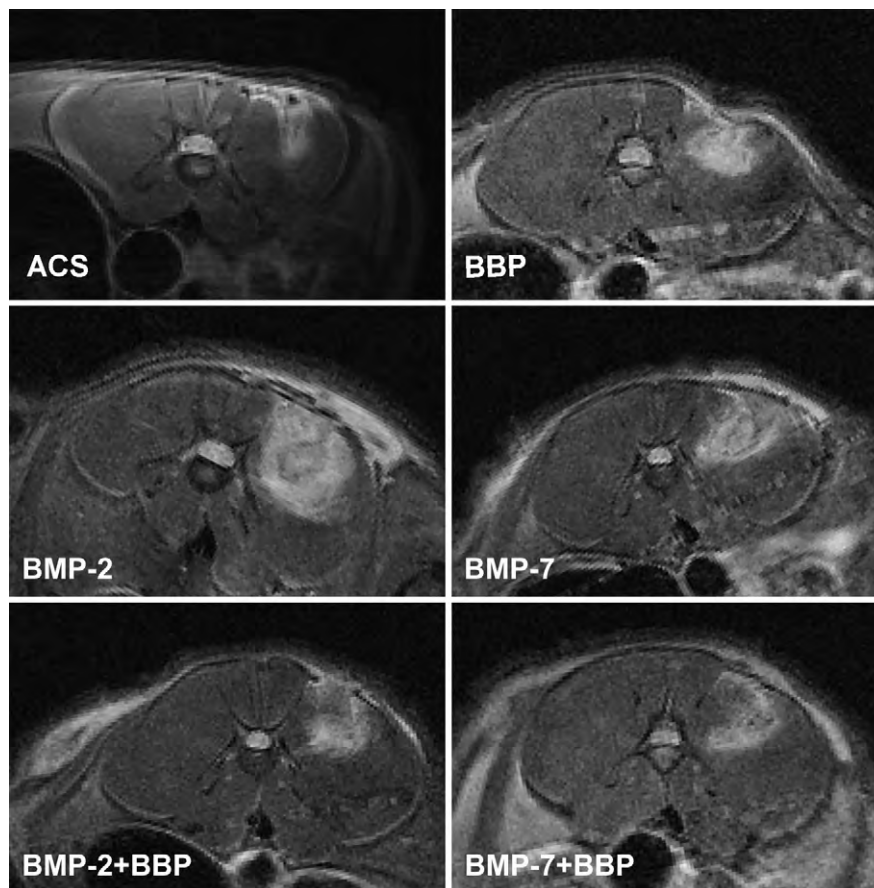
Fig. 2. Magnetic resonance images showing examples of specific implants: ACS, BBP, rhBMP-2, rhBMP-7, BBP+rhBMP-2, and BBP+rhBMP-7. ACS, absorbable collagen sponge; BBP, bone morphogenetic protein–binding peptide; rhBMP, recombinant human bone morphogenetic protein.

Table 1
Inflammatory volume measured by magnetic resonance imaging after intramuscular and subcutaneous implantations of different materials

| Type of implants	Intramuscular				Subcutaneous			
	3 h	2 d	4 d	7 d	3 h	2 d	4 d	7 d
ACS	104.3±8.3	126.7±17.7	69.9±123.4	47.2±119.4	111.3±19.6	67.2±3.9.9	49.7±115.2	48.1±113.9
BBP	213.4±12.8	179.8±5.4	162.1±8.2	81.7±11.8	179.7±14.4	129.1±16.1	102.8±17.8	89.3±14.2
BMP2	311.3±47.2	573.2±80.7	365.4±61.7	226.5±46.3	277.7±75.1	259.1±59.3	198.9±67.4	123.1±32.7
BBP+BMP2	233.3±81.1	260.3±26.5	210.2±20.6	161.1±42.3	208.0±28.4	161.3±28.7	145.3±18.7	115.8±25.8
BMP7	264.7±55.1	382.1±69.7	258.9±47.9	129.9±21.9	223.1±31.9	209.8±59.5	159.9±51.2	94.1±17.1
BBP+BMP7	232.5±31.8	248.1±40.2	178.2±26.1	118.9±29.8	222.2±35.6	176.4±21.0	139.3±27.8	90.1±11.3

ACS, absorbable collagen sponge; BBP, bone morphogenetic protein–binding peptide; BMP2, recombinant human bone morphogenetic protein 2; BMP7, recombinant human bone morphogenetic protein 7.

Data are shown as mean±standard deviation (mm^3). N=5 for all treatment groups.

but the differences achieved statistical significance only at 2 days (Fig. 3D, Tables 1 and 2).

Measurement of inflammatory mass volumes in SC implants with gross morphometric analyses

Granuloma-like masses developed in all implants after SC implantation (Fig. 4A1–A6, Table 3). The sizes of the mass in the ACS alone, BBP alone, rhBMP-2 alone, rhBMP-2 plus BBP, rhBMP-7 alone, and rhBMP-7 plus BBP groups were 47.7±4.2, 53.8±7.2, 103.1±11.3, 73.0±8.6, 86.2±19.7, and 56.8±10.1 mm^3, respectively (Table 3). The mean mass size of BBP alone group was significantly smaller than that of the rhBMP-2 alone group, and that of the rhBMP-2 plus BBP group was also significantly smaller than that of the rhBMP-2 alone group (p=.001, p=.001; Fig. 4B).

Furthermore, the mean mass size for the BBP alone group was significantly smaller than that for the rhBMP-7 alone group (p=.001). However, although the mean mass volume of the rhBMP-7 plus BBP group was smaller than that of the rhBMP-7 alone group, the difference did not achieve statistical significance (Fig. 4B).

Measurement of inflammatory mass volumes in IM implants with microscopic analyses

The inflammatory zone surrounding the various IM implants showed different areas of host reactions (Fig. 5A1–A6). There were histiocytes, fibrocytes (two black arrows), and granulation tissue surrounding implanted ACS fibril (red block arrow) in all treatment groups (Fig. 5B). The area (mm^2) of the inflammatory zone surrounding the implants in the ACS alone, BBP alone, rhBMP-2 alone, rhBMP-2 plus BBP, rhBMP-7 alone, and rhBMP-7 plus BBP groups were 3.83±0.6, 4.55±0.6, 10.25±1.2, 7.81±0.7, 7.88±0.9, and 5.30±0.9, respectively (Table 3). The mean area (mm^2) of the inflammatory zones of the BBP alone group was significantly smaller than those of the rhBMP-2 and rhBMP-7 alone groups (p=.002, p=.007, respectively). In addition, the mean areas (mm^2) of the inflammatory zones of the rhBMP-2 plus BBP and rhBMP-7 plus BBP groups were also significantly smaller than those of the rhBMP-2 alone and rhBMP-7 alone groups (p=.033, p=.029, respectively; Fig. 5C).

Discussion

Although early industry-sponsored trials have reported excellent clinical fusion results from the use of rhBMP-2 and rhBMP-7 (osteogenic protein-1) [20,21], controversy remains regarding the potential complications that can occur [4,10,11,22–24]. This is of particular concern when used off-label in the cervical spine because of the potential for swelling of the soft tissues, which can lead to dysphagia, airway compression, and potential neurological impairment. Reports of these complications led to a warning by the US Food and Drug Administration in July 2008 regarding the use of the BMPs [9–11].

Table 2
The p values for comparisons between groups from magnetic resonance imaging–based measurements shown in Table 1

Comparisons	Intramuscular				Subcutaneous			
	3 h	2 d	4 d	7 d	3 h	2 d	4 d	7 d
BBP+BMP2: BMP2	<.001	<.001	<.001	<.001	<.01	<.01	<.01	<.01
BBP+BMP7: BMP7	.160*	<.05	<.01	.210*	.874*	<.05	.487*	.687*
BBP: ACS	<.001	<.01	<.001	<.05	<.001	<.001	<.01	<.01
BBP: BMP2	<.01	<.001	<.01	<.001	<.05	<.05	<.01	<.05
BBP: BMP7	<.05	<.01	<.01	<.001	<.01	<.05	<.05	.810*
BBP: BBP+BMP2	<.01	<.001	<.001	.915*	<.001	<.01	<.05	<.01
BBP: BBP+BMP7	.249*	<.001	.222*	<.05	<.05	<.01	<.05	.932*

BBP, bone morphogenetic protein–binding peptide; BMP2, recombinant human bone morphogenetic protein-2; BMP7, recombinant human bone morphogenetic protein-7; ACS, absorbable collagen sponge.

* denotes that there is no statistically significance between the two groups.
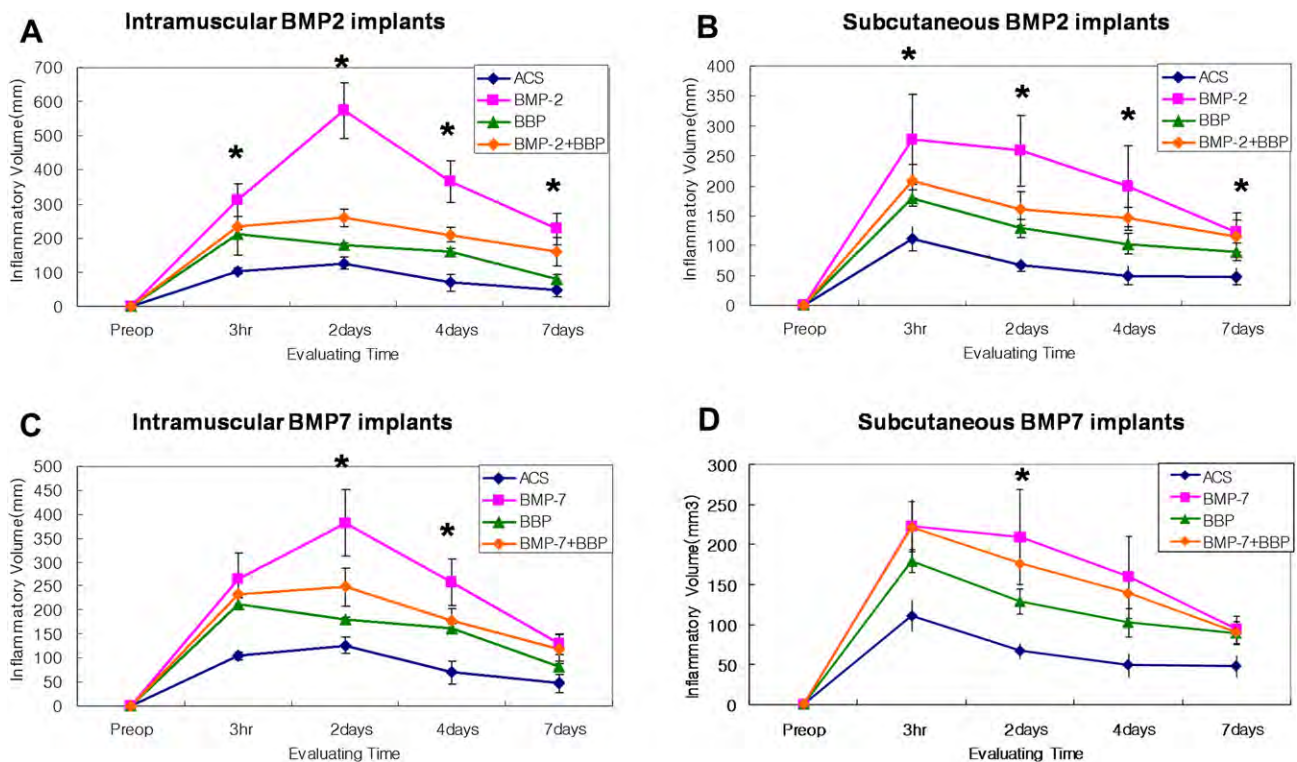
Fig. 3. Mean soft-tissue edema volumes for intramuscular and subcutaneous implants at 2 hours and at 2, 4, and 7 days after surgery. (A) Intramuscular BMP-2. (B) Subcutaneous BMP-2. (C) Intramuscular BMP-7. (D) Subcutaneous BMP-7. * denotes a statistically significant difference for the comparison of BMP-2 alone versus BMP-2 plus bone BBP, and BMP-7 alone versus BMP-7 plus BBP. BMP, bone morphogenetic protein; BBP, bone morphogenetic protein–binding peptide.

The inflammatory reaction to BMPs in cervical and lumbar spine fusion surgery is not fully understood; however, postoperative radiculitis and painful seroma have been reported not infrequently [25–28]. Previous reports [25–28] have asserted that these complications are related with inflammatory reaction of BMPs to local tissues such as the surrounding muscle and nervous tissue. The management of theses complications has varied depending on the degree of patient's symptoms from simple observation to required decompressive surgery [27,28]. It is likely that adverse reactions in cervical surgery have received more attention because of the presence of critical vascular and airway structures in a confined space in the neck.

To study and gain a further understanding of this inflammatory response, we have developed both in vitro and in vivo rodent models [12,13]. Previous studies using our in vivo model demonstrated that implantation of rhBMP-2 or rhBMP-7 resulted in a peak edema volume at 2 days after surgery in the case of IM implantation and 3 hours after surgery in the case of SC implantation [12,13].

Furthermore, the magnitude of the inflammatory reaction was demonstrated to be dose dependent [12,13]. Other animal studies using BMPs combined with the BBP have shown that smaller doses of BMPs are as effective in achieving fusion as are larger doses of BMPs when delivered in a collagen matrix containing BBP [14–16]. These previous studies demonstrate that the development of improved BMP delivery systems may have the potential to reduce the dose of BMP needed for fusion and possibly reduce the dose-dependent adverse reactions. The present study is an attempt to address the possibility of decreasing the inflammatory response using combinations of BMP and BBP.

Bone morphogenetic protein–binding peptide is a synthetic, cyclic, 19 amino acid peptide, the structure of which is based on the BMP/transforming growth factor-β–binding domain of a protein that is known both as the 18.5 kDa component of Urist ''BMP/noncollagenous protein'' and as a 18.5 kDa proteolytic fragment of secreted phosphoprotein 24 (spp24) [14]. A similar binding site with homology to the transforming growth factor-β II receptor (referred to as the TRH 1 domain) is found in other BMP-2–binding proteins such as fetuin [14,15]. This synthetic peptide (BBP) has been shown to bind BMP-2, BMP-7, and other members of the transforming growth factor-β family of cytokines [14,15] and to enhance and accelerate BMP-2–induced bone formation in a heterotopic bone forming assay [14] and to enhance BMP-2- and BMP-7–induced bone formation in a rodent model of spinal fusion [15,16]. These studies have shown that the use of BBP-based carriers significantly reduced (from 70% to 90% in different models) doses of BMPs to achieve the same osteogenic response [14–16]. The hypothesized mechanism of action for the BBP-based carrier systems is that they allow for a ''slow release'' of cytokine. This hypothesis is supported by studies that have
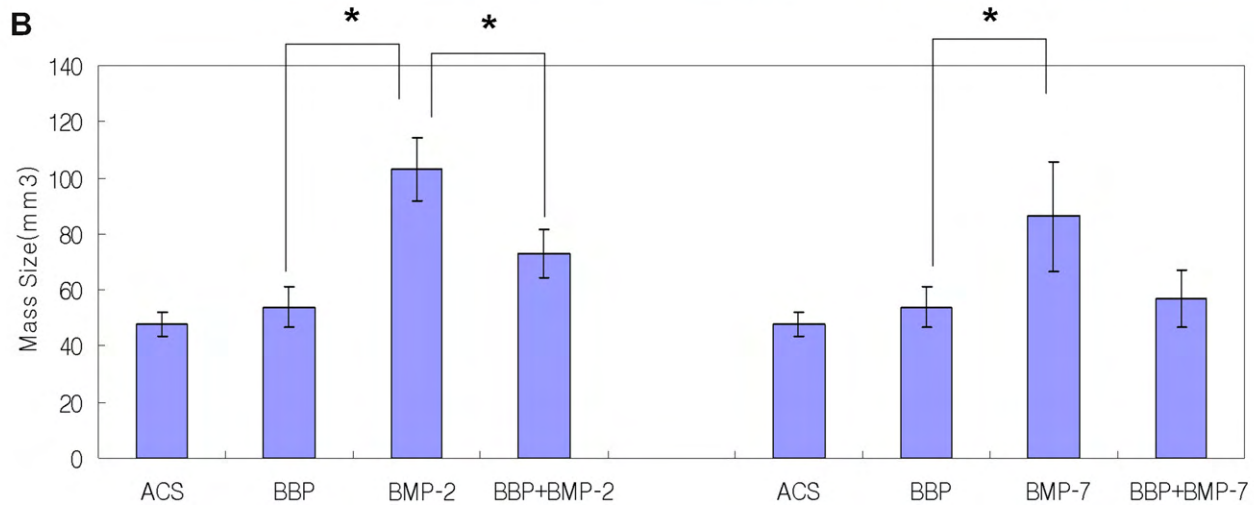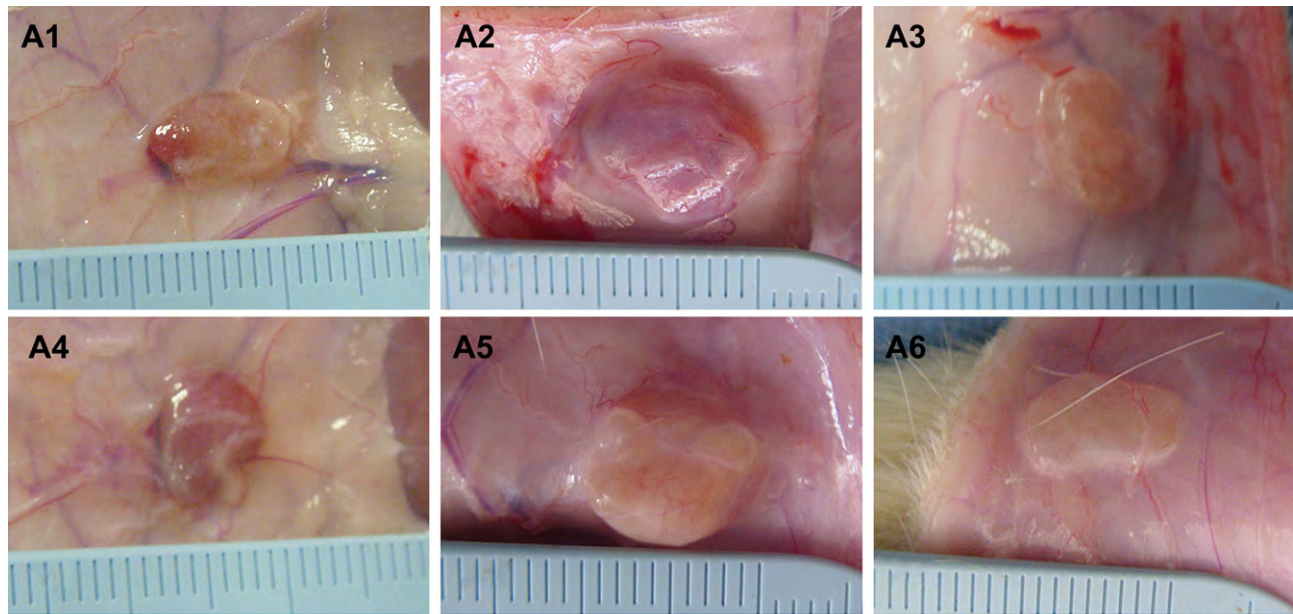
Fig. 4. Panel A: Gross morphological findings of subcutaneous implants of different implant groups. (A1) ACS alone. (A2) BMP-2 alone. (A3) BMP-2 plus BBP. (A4) BBP alone. (A5) BMP-7 alone. (A6) BMP-7 plus BBP. Panel B: Comparison of volumes of inflammatory masses. * denotes a statistically significant difference between both BBP+rhBMP-2/7 and rhBMP-2/7 implantations. ACS, absorbable collagen sponge; BMP, bone morphogenetic protein; BBP, bone morphogenetic protein–binding peptide; rhBMP, recombinant human bone morphogenetic protein.

demonstrated that BBP increases the residence time of BMP-2 in a collagen implant [15]. For example, at 7 days, 53% of the BMP-2 remained at the implant site in the carrier containing BBP, whereas only 28% of the BMP-2 remained in the carrier without BBP [15].

In this study, we have tested the efficacy of a BBP-based carrier system to reduce the inflammatory response to rhBMP-2 and rhBMP-7 in a well-defined rodent model of soft-tissue inflammation. The MRI-based measurements of soft-tissue edema volume demonstrated that the soft-tissue

Table 3
Inflammatory mass volume of subcutaneous implants by gross morphometric analysis and inflammatory zone area of intramuscular implants by microscopic analysis

Inflammation	ACS	BBP	BMP2	BBP+BMP2	BMP7	BBP+BMP7
Subcutaneous inflammatory mass volume (mm^3)	47.7±4.2	53.8±7.2	103.1±11.3	73.0±8.6	86.2±19.7	56.8±10.1
Intramuscular inflammatory zone area (mm^2)	3.83±0.6	4.55±0.6	10.25±1.2	7.81±0.7	7.88±0.9	5.30±0.9

ACS, absorbable collagen sponge; BBP, bone morphogenetic protein–binding peptide; BMP2, recombinant human bone morphogenetic protein 2; BMP7, recombinant human bone morphogenetic protein 7.

Data are shown as mean±standard deviation. N=5 for all treatment groups.

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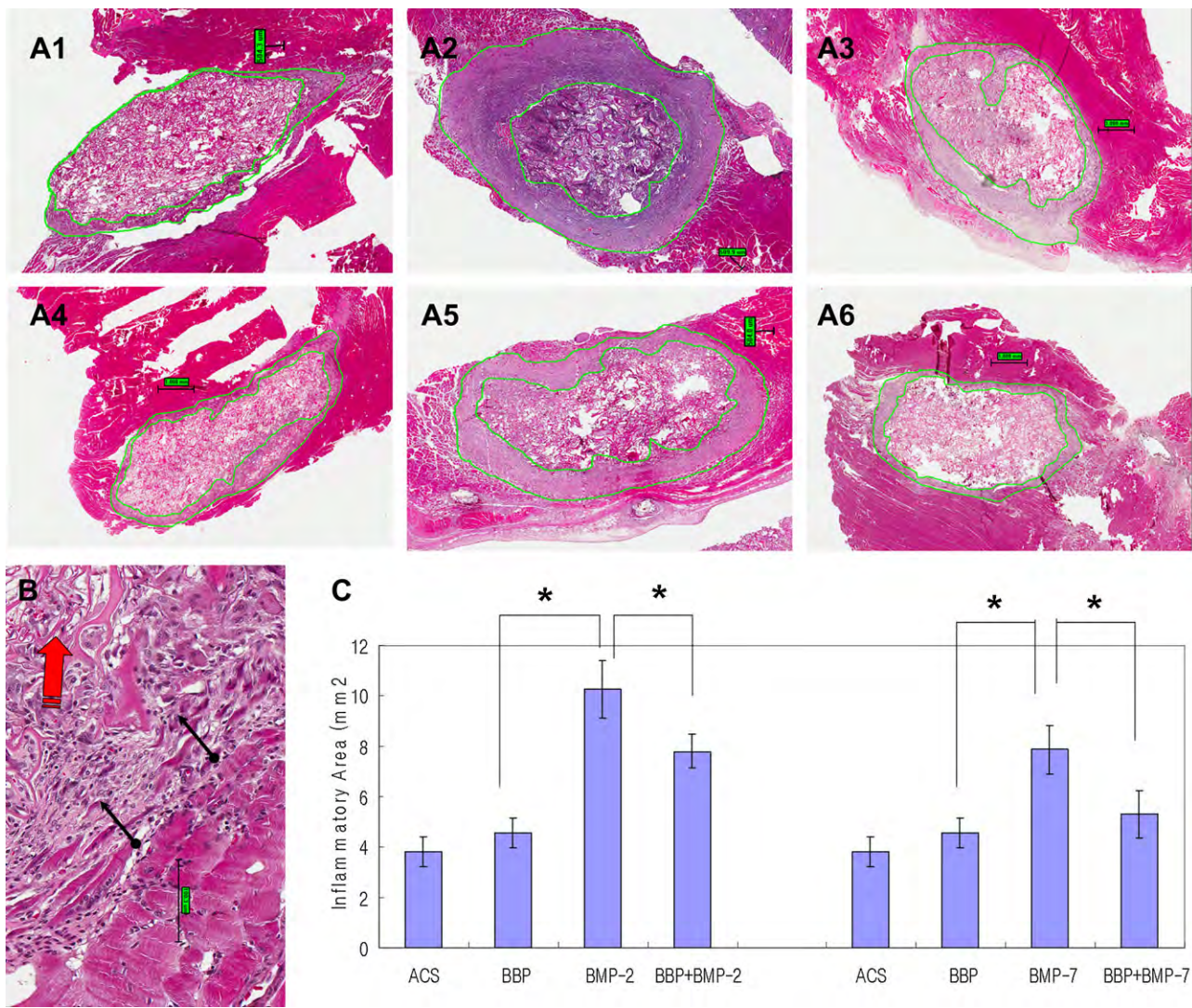
Fig. 5. Panel A: Microscopic findings (original magnification, ×10; scale bar, 500 μm) for intramuscular implants: (A1) ACS alone. (A2) rhBMP-2 alone. (A3) BMP-2 plus BBP. (A4) BBP alone. (A5) rhBMP-7 alone. (A6) rhBMP-7 plus BBP. In the images of Panel A, the two green circles show the area measurement (mm²) method for the determination of soft-tissue inflammatory mass using Aperio ImageScope software (scale bar, 500 μm). The area of the actual inflammatory zone was calculated by subtracting the area of inner zone from the area of the outer zone. Panel B: An illustrative photomicrograph of an implant showing the presence of histiocytes, fibroblasts (two black arrows), and granulation tissue surrounding implanted ACS fibril (red block arrow) (original magnification, ×200; scale bar, 50 μm). Panel C: Inflammatory mass areas for the different treatment groups. * denotes a statistically significant difference for the comparisons of rhBMP-2 alone versus rhBMP-2 plus BBP and for rhBMP-7 alone versus rhBMP-7 plus BBP. ACS, absorbable collagen sponge; BMP, bone morphogenetic protein; BBP, bone morphogenetic protein–binding peptide; rhBMP, recombinant human bone morphogenetic protein.

edema volume in the rhBMP-2 plus BBP and rhBMP-7 plus BBP treatment groups were both significantly lower than those of rhBMP-2 alone and rhBMP-7 alone treatment groups at all time points. This is especially apparent at the 2-day time point in the IM implantations and the 3-hour time point in the SC implantations. Interestingly, the magnitude of the inflammatory response to rhBMP-7 was consistently lower than that to rhBMP-2 (Fig. 3, Tables 1–3), but the degree of relative reduction of inflammatory mass with BBP was approximately the same. Furthermore, although the overall trend is apparent, more time points in the BMP-7 treatment groups did not reach statistical significance. In addition, the binding of BMP-2 and BMP-7 to BBP and spp24 is somewhat different, with BMP-7 having

a somewhat less affinity than BMP-2. However, caution must be taken to not overinterpret these differences as these studies with five animal subjects per treatment group are only statistically powered to detect large differences. It is also interesting to note that the inflammatory response to rhBMP-7 consistently peaked earlier (3 hours) than did the response to rhBMP-2 (2 days) (Fig. 3, Tables 1 and 2). Further studies will be required to determine if this represents a clinically significant difference. An additional limitation of this small study would be a systematic inability to detect low-frequency major or catastrophic events with the BMP/BBP combination.

The results of the gross and microscopic examinations of SC and IM inflammatory masses in general confirmed the

results of the MRI studies. Although the overall pattern is consistent, the differences at some time points are not statistically significant. Studies that include larger numbers of animal subjects would be required to precisely define these differences. In the microscopic examination of the IM implants, a similar response was observed in all treatment groups. This response consisted primarily of histiocyte, fibrocyte, and granulation tissue. These results are similar to those reported in the systematic study of tissue response to biomaterials [29,30].

Conclusion

Bone morphogenetic protein–binding peptide may reduce the inflammatory response induced by both rhBMP-2 and rhBMP-7 as seen in this small trial in a rodent model of inflammation. The overall inflammatory response to BMP-2 appeared to be greater than that to BMP-7, but this finding needs to be confirmed by studies with larger numbers of animal subjects. The degree of the reduction of the inflammatory response with the use of BBP was roughly the same for both cytokines. Carriers of this type may allow for the use of optimized doses on BMPs that may improve outcomes. Further preclinical studies are required.

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Journal Reports

The Spine Journal editors present abstracts from selected articles which may be of interest to *TSJ* readers.

Gluteal-sparing approach for posterior iliac crest bone graft: description of a new technique and assessment of morbidity in ninety-two patients after spinal fusion. Merritt AL, Spinnicke A, Pettigrew K, Alamin TF. Spine 2010;35(14):1396–400

SUMMARY: The objective of this study was to assess the local morbidity experienced by patients undergoing posterior iliac crest bone graft using a limited exposure wherein the surgeon exposes the PSIS and a few centimeters laterally, creates a small osseous window, and removes cancellous bone from between the tables of the ilium. While the technique is described as 'new', it is only new to publication and has been used extensively for years in the US, Europe, and especially Australia where Rob Fraser's group popularized it. The importance of the paper, however, does not rest on the novelty of the technique; but rather on the reported results. The authors found that in 92 patients available for an average follow-up of two years, 88% reported no difference in pain or less pain over the graft site than over their contralateral PSIS. Twelve percent described more pain over the harvest site, but eight percent described more over the contralateral side—no statistical difference. It is important to note that 28 patients undergoing the technique were lost to follow-up, their morbidities are unknown, and had they been included may have impacted the significance of the findings. Morbidity associated with posterior ICBG has been a primary motivation for the use of graft substitutes such as BMPs. However, many of the previously published papers on the subject have significant methodological flaws which limit the validity of their conclusions; have been reported by authors with conflicts of interest related to graft replacement therapies which might bias their reports; and do not clarify the technique of graft attainment which might be vital to associated morbidity rates. This subject requires further investigation given the costs and emerging morbidities associated with the increasing use of graft substitutes coupled with the findings in this study.

Does the location of low back pain predict its source? Depalma MJ, Ketchum JM, Trussell BS, Saullo TR, Slipman CW. PM R 2011;3(1):33–9

OBJECTIVE: To evaluate the predictive utility of the pattern of low back pain (LBP) in detecting the source of LBP as internal disk disruption (IDD), facet joint pain (FJP), or sacroiliac joint pain (SIJP).
DESIGN: Retrospective chart review.
SETTING: University spine center.
PATIENT SAMPLE: A total of 170 cases from 156 patients presenting with LBP whose low back disorder was definitively diagnosed. The mean age was 54.4 years (SD, 16.2) and median duration of LBP was 12 months (interquartile ranges, 6–32).
METHODS: Charts of consecutive LBP patients who underwent definitive diagnostic spinal procedures including provocation diskography, facet joint blocks, and sacroiliac joint blocks were retrospectively reviewed. Each patient with LBP was queried as to the exact location of their LBP: midline, defined as in-line with the spinous processes, and/or paramidline, defined as lateral to 1 fingerbreadth adjacent to the midline.
OUTCOME MEASURES: In patients with a definitive diagnosis for the source of LBP, the proportion of each diagnosed source of pain was calculated. $\chi(2)$ tests were used to identify differences in the percentages of midline and paramidline LBP among the groups of patients testing positive for IDD, FJP, or SIJP. Diagnostic measures of sensitivity, specificity, positive and negative predictive values, diagnostic accuracy, and likelihood ratios of positive and negative tests using the presence/absence of midline and paramidline pain for the diagnosis of IDD, FJP, and SIJP were estimated.
RESULTS: With cases of IDD, significantly greater percentages of patients reported midline LBP (95.8%; $\chi(2) = 101.4$, df = 2, p<.0001) as compared with cases of FJP (15.4%) or SIJP (12.9%). In cases of IDD, significantly lower percentages of patients reported paramidline pain (67.3%; $\chi(2) = 16.1$, df = 2, p=.0003) as compared with cases of FJP (95.0%) or SIJ (96.0%). In cases of IDD, significantly greater percentages of patients reported midline LBP (95.8%; $\chi(2) = 101.4$, df = 2, p<.0001) as compared with cases of FJP (15.4%) or SIJP (12.9%). The specificity of midline LBP for IDD, FJP, and SIJP was 74.8% (95% CI = 65.0%–82.9%), 28.0% (20.1%–37.0%), and 36.0% (28.0%–44.5%), respectively. The negative predictive value of paramidline LBP for IDD, FJP, and SIJP was 29.2% (95% CI = 12.6%–51.1%), 91.7% (73.0%–99.0%), and 95.8% (78.9%–99.9%). The diagnostic accuracy of midline LBP for IDD, FJP, and SIJP was 83.5%, 24.1%, and 31.8%, respectively.
CONCLUSIONS: The presence of midline LBP increases the probability of lumbar IDD and reduces the probability of symptomatic FJ and SIJ dysfunction. The presence of isolated paramidline LBP increases the probability of symptomatic FJ or SIJ but mildly reduces the likelihood of lumbar IDD.

Low pressure pain thresholds are associated with, but does not predispose for, low back pain. O'Neill S, Kjær P, Graven-Nielsen T, Manniche C, Arendt-Nielsen L. Eur Spine J 2011 Apr 22. [Epub ahead of print]

Chronic pain is often associated with hyperalgesia in cross-sectional studies. In the present study, a random cohort of 40-year-old individuals (n=264)

from the general population was assessed for low back pain (LBP) status and pressure pain threshold (PPT), with follow-up assessment 4 and 8 years later. Low PPT at baseline as a potential risk factor for the development of LBP was investigated longitudinally and the association between LBP and hyperalgesia was studied cross-sectionally at baseline and 8-year follow-up. Generalized (p<.03) and localized pressure hyperalgesia (p<.02) was found in participants with long-lasting LBP, but not with recent LBP (p>.08). Of the participants without recent or long-lasting LBP, those with a low PPT at baseline (lower 10% percentile) had no increased risk of developing LBP (p>.05). The findings indicate that PPT decreases as a consequence of long-lasting pain, whereas a low PPT seems not to constitute a separate risk factor for the development of LBP.

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Symptoms of depression and stress mediate the effect of pain on disability. Hall AM, Kamper SJ, Maher CG, Latimer J, Ferreira ML, Nicholas MK. Pain 2011;152(5):1044–51

The mechanism or mechanisms involved in the development of pain-related disability in people with low back pain is unclear. Psychological distress has been identified as one potential pathway by which an episode of pain influences the development of persistent disabling symptoms; however, the relationship has not been formally investigated. This study investigated the causal relationship between pain and disability via psychological distress (and its components depression, stress, and anxiety) by using mediation path analysis. The study sample included 231 participants with subacute low back pain (6 to 12 weeks' pain duration) who had been recruited for an exercise-based randomised, controlled trial. All participants completed self-report assessments of pain (0–10 numerical rating scale), disability (Roland Morris Disability Questionnaire), and psychological distress (Depression Anxiety and Stress Scale) at baseline and again at 2 follow-up time points (6 and 12 weeks after baseline). The results of the mediation analysis suggest that approximately 30% of the relationship between subacute pain and later disability is dependent on the level of patients' psychological distress. The finding that psychological distress only partially (30%) mediated the pain-disability relationship indicates that other factors should also be explored. Further analysis into the components of psychological distress revealed that the symptoms of depression and stress, but not anxiety, are responsible for mediation of the pain-disability relationship. These findings provide an opportunity to decrease the risk of long-term disability through early identification and management of depressive and stress symptoms. Psychological distress symptoms at 6 weeks in patients with low back pain influences future disability. Symptoms of depression and stress, but not anxiety, are responsible for mediation of the pain-disability relationship.

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Survival prognostic factors and clinical outcomes in patients with spinal metastases. Pointillart V, Vital JM, Salmi R, Diallo A, Quan GM. J Cancer Res Clin Oncol 2011;137(5):849–56. Epub 2010 Sep 4

PURPOSE: In patients with metastatic disease to the spine, patient selection for surgery and the extent of surgery to perform thereafter remains controversial, with the patient's survival prognosis the most important consideration. For this reason, we conducted a prospective study investigating prognostic factors and clinical outcomes in a consecutive series of patients with vertebral metastases.

METHODS: A total of 142 consecutive patients with vertebral metastases referred to us for consideration of surgery were prospectively enrolled into this study. Of these, 118 patients subsequently underwent palliative surgery for intractable pain or radiculopathy, bony instability or spinal cord compression. Patients were followed up for 12 months or until death. A multivariate analysis of the patients was conducted using the Cox proportional hazards model. The survival predictive accuracy of the Tokuhashi score was also investigated. For the patients who underwent surgery, pre- and post-operative outcomes were assessed on pain, neurological deficit, function and overall quality of life.

RESULTS: The overall 12-month mortality rate was 50.7% and the median survival was 5 months. Multivariate analysis showed that independent prognostic factors for survival after spinal metastases include primary tumour type, Karnofsky functional status, ASA score and pain. Neither the original nor revised Tokuhashi scores were reliable in predicting survival in our European population. In the patients who underwent operative intervention, there was an immediate and prolonged improvement in pain, neurological deficit, function and quality of life in the majority of cases.

CONCLUSIONS: The potential for rapid and maintained improvement in clinical outcome and quality of life should be considered when selecting patients with metastatic disease to the spine for surgery rather than basing decisions solely on survival prognostic factors comprising current scoring systems.

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Correlation between disability and MRI findings in lumbar spinal stenosis: a prospective study of 109 patients operated on by decompression. Sigmundsson FG, Kang XP, Jönsson B, Strömqvist B. Acta Orthop. 2011;82(2):204–10. Epub 2011 Mar 24

BACKGROUND AND PURPOSE: MRI is the modality of choice when diagnosing spinal stenosis but it also shows that stenosis is prevalent in asymptomatic subjects over 60. The relationship between preoperative health-related quality of life, functional status, leg and back pain, and the objectively measured dural sac area in single and multilevel stenosis is unknown. We assessed this relationship in a prospective study.

PATIENTS AND METHODS: The cohort included 109 consecutive patients with central spinal stenosis operated on with decompressive laminectomy or laminotomy. Preoperatively, all patients completed the questionnaires for EQ-5D, SF-36, Oswestry disability index (ODI), estimated walking distance and leg and back pain (VAS). The cross-sectional area of the dural sac was measured at relevant disc levels in mm^2, and spondylolisthesis was measured in mm. For comparison, the area of the most narrow level, the number of levels with dural sac area <70 mm^2, and spondylolisthesis were studied.

RESULTS: Before surgery, patients with central spinal stenosis had low HRLQoL and functional status, and high pain levels. Patients with

multilevel stenosis had better general health (p=.04) and less leg and back pain despite having smaller dural sac area than patients with single-level stenosis. There was a poor correlation between walking distance, ODI, the SF-36, EQ-5D, and leg and back pain levels on the one hand and dural sac area on the other. Women more often had multilevel spinal stenosis (p=.05) and spondylolisthesis (p<.001). Spondylolisthetic patients more often had small dural sac area (p=.04) and multilevel stenosis (p=.06).

INTERPRETATION: Our findings indicate that HRQoL, function, and pain measured preoperatively correlate with morphological changes on MRI to a limited extent.

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Are persistently symptomatic vertebral compression fractures associated with abnormal inflammatory profiles? A prospective study. Golish SR, Hanna LS, Cuellar JM, et al. J Spinal Disord Tech 2011;24(2):121–5

STUDY DESIGN: A case-control study with prospectively collected samples for laboratory analysis in a series of patients with spinal fragility fractures and a series of patients without fracture who underwent fusion for LBP.

OBJECTIVE: Was an exploratory data analysis for candidate cytokine biomarkers present in the fracture milieu of patients with persistent back pain associated with vertebral compression fracture.

SUMMARY OF BACKGROUND DATA: Lumbar and thoracic compression fractures are common. Little is known about the presence of inflammatory mediators within fractured vertebra in the clinical setting.

METHODS: Thirty patients diagnosed with a single thoracic or lumbar compression fracture were treated with single level vertebroplasty. At the time of intervention, needle aspiration was carried out at the fractured level. A multiplexed bead assay was used to assess the presence of 27 different cytokines and inflammatory mediators. A control group consisted of needle aspiration samples of 30 lumbar vertebra from 13 patients with chronic pain but no fracture undergoing open instrumented fusion.

RESULTS: Thirty patients with 30 fractures consisted of 23 female and 7 male with a mean age of 77.5 years (SD 13.6; range 42 to 97) and a mean of 3.9 weeks of pain (SD 3.1; range 1 to 12). The highest levels of inflammatory mediators were (in order): IL-1 receptor antagonist, PDGF, RANTES, IP-10, IL-8, and eotaxin. These mediators were present at concentrations >200 pg/mL. Compared with controls with chronic pain, significant differences were present for 4 mediators: TNF, MIP-1b, IL-9, and IL-12. The panel of these 4 markers was 93.3% specific and 66.7% sensitive for fracture compared with the control group.

CONCLUSIONS: Inflammatory mediators are present in needle aspirates of symptomatic vertebral compression fractures. Some of these mediators show different levels than in patients with chronic pain but no fracture.

LEVEL OF EVIDENCE: Diagnostic level of evidence II.

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Outcome of lumbar epidural steroid injection is predicted by assay of a complex of fibronectin and aggrecan from epidural lavage. Golish S, Hanna LS, Bowser RP, Montesano PX, Carragee EJ, Scuderi GJ. Spine 2011 Feb 9. [Epub ahead of print]

STUDY DESIGN: A single center, prospective, consecutive case series of patients undergoing epidural lavage prior to treatment of radiculopathy due to lumbar disc herniation.

OBJECTIVE: To determine if a novel complex of fibronectin and aggrecan predicts clinical response to epidural steroid injection (ESI) for the indication of radiculopathy from lumbar herniated nucleus pulposus (HNP).

SUMMARY OF BACKGROUND DATA: Epidural steroid injection (ESI) for lumbar radiculopathy due to herniated nucleus pulposus (HNP) is widely used despite variable effectiveness for this indication. With increased attention aimed at cost containment, it would be beneficial to identify those in whom ESI may be helpful. There are currently no accurate diagnostic tests to predict response to ESI in back pain and sciatica syndromes. We have previously investigated biomarkers of disc degeneration associated with radiculopathy.

METHODS: We embarked to determine if a molecular complex of fibronectin and aggrecan predicts clinical response to ESI for the indication of radiculopathy from HNP. This prospective study was conducted at a single center and included 26 patients with radiculopathic pain and MRI positive for HNP who elected ESI. Epidural lavage with physiologic saline was performed immediately prior to ESI. The lavage fluid was assayed for the fibronectin-aggrecan complex using a heterogeneous enzyme-linked immunosorbent sandwich assay (ELISA). The results were compared with the interval improvement in the physical component summary (PCS) score of the Medical Outcomes Study Short Form-36 instrument (SF-36) after injection compared with baseline.

RESULTS: The mean improvement from baseline PCS in patients with the fibronectin-aggrecan complex was 22.9 (standard deviation 12.4) and without the complex was 0.64 (standard deviation 3.97; p<.001). Differences in total SF-36 improvement were also highly significant (p<.001). The presence of the fibronectin-aggrecan complex predicts a clinically significant increase in PCS after lumbar ESI by receiver-operating-characteristic (ROC) analysis (area under the curve=0.97; p<.001). There was no significant difference in age (p=.25), gender (p=.84), laterality (p=.06), lumbar spinal level (p=.75), or payer type (worker's compensation vs. private insurance; p=.90) between groups with and without the marker.

CONCLUSION: A molecular complex of fibronectin and aggrecan predicts response to lumbar ESI for radiculopathy with HNP. The biomarker is accurate, objective, and is not affected by demographic or psychosocial variables in this series. Level of Evidence: Diagnostic level of evidence II.

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doi: 10.1016/j.spinee.2011.05.028

Evidence for an inherited predisposition to lumbar disc disease. Patel AA, Spiker WR, Daubs M, Brodke D, Cannon-Albright LA. J Bone Joint Surg Am 2011;93(3):225–9

BACKGROUND: A genetic predisposition for the development of symptomatic lumbar disc disease has been suggested by several twin sibling studies and subsequent genetic marker studies. The purpose of the present study was to define population-based familial clustering among individuals with a diagnosis of, or treated for, lumbar disc herniation or disc degeneration.

METHODS: The Utah Population Database allows analysis of combined health and genealogic data for over one million Utah residents. We used the International Classification of Diseases, Ninth Revision, diagnosis

codes entered in patient records to identify patients with a diagnosis of either lumbar disc herniation or lumbar disc degeneration and genealogic data. The hypothesis of excess relatedness (familial clustering) was tested with use of the Genealogical Index of Familiality, which compares the average relatedness of affected individuals with expected population relatedness. Relative risks in relatives were estimated by comparing rates of disease in relatives with expected population rates (estimated from the relatives of matched controls). This methodology has been previously reported for other disease conditions but not for spinal diseases.

RESULTS: The Genealogical Index of Familiality test for 1264 patients with lumbar disc disease showed a significant excess relatedness ($p<.001$). Relative risk in relatives was significantly elevated in both first-degree (relative risk, 4.15; $p<.001$) and third-degree relatives (relative risk, 1.46; $p=.027$).

CONCLUSIONS: Excess relatedness of affected individuals and elevated risks to both near and distant relatives was observed, strongly supporting a heritable contribution to the development of symptomatic lumbar disc disease.

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doi: 10.1016/j.spinee.2011.05.029

The outcome of decompression surgery for lumbar herniated disc is influenced by the level of concomitant preoperative low back pain. Kleinstueck FS, Fekete T, Jeszenszky D, et al. Eur Spine J 2011 Jan 12. [Epub ahead of print]

Decompression surgery is a common and generally successful treatment for lumbar disc herniation (LDH). However, clinical practice raises some concern that the presence of concomitant low back pain (LBP) may have a negative influence on the overall outcome of treatment. This prospective study sought to examine on how the relative severity of LBP influences the outcome of decompression surgery for LDH. The SSE Spine Tango System was used to acquire the data from 308 patients. Inclusion criteria were LDH, first-time surgery, maximum 1 affected level, and decompression as the only procedure. Before and 12 months after surgery, patients completed the multidimensional Core Outcome Measures Index (COMI; includes 0–10 leg/buttock pain (LP) and LBP scales); at 12 months, global outcome was rated on a Likert scale and dichotomised into "good" and "poor" groups. In the "good" outcome group, mean baseline LP was 2.8 (SD 3.1) points higher than LBP; in the "poor" group, the corresponding value was 1.1 (SD 2.9) ($p<.001$ between groups). Significantly fewer patients with back pain as their "main problem" had a good outcome (69% good) when compared with those who reported leg/buttock pain (84% good) as the main problem ($p=.04$). In multivariate regression analyses (controlling for age, gender, co-morbidity), baseline LBP intensity was

a significant predictor of the 12-month COMI score, and of the global outcome (each $p<.05$) (higher LBP, worse outcome). In conclusion, patients with more back pain showed significantly worse outcomes after decompression surgery for LDH. This finding fits with general clinical experience, but has rarely been quantified in the many predictor studies conducted to date. Consideration of the severity of concomitant LBP in LDH may assist in establishing realistic patient expectations before the surgery.

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Pain is associated with regional grey matter reduction in the general population. Ruscheweyh R, Deppe M, Lohmann H, et al. Pain 2011;152(4):904–11. Epub 2011 Feb 5.

Regional decreases in grey matter volume as detected by magnetic resonance imaging-based volumetry have been reported in several clinical chronic pain cohorts. Here, we used voxel-based morphometry in a nonclinical cohort to investigate whether grey matter alterations also occur in older individuals (aged 40–85 years) from the general population. Based on self-report of pain, we identified 31 pain-free controls, 45 subjects with ongoing pain (low back pain, headache, or lower extremity joint pain) who had at least moderate pain on more than 3 days/month, and 29 individuals with past pain (stopped for >12 months). Relative to controls, the ongoing pain group showed regional grey matter volume decreases, predominantly in cingulate, prefrontal, and motor/premotor regions. No grey matter volume decreases were found in the group with pain that had stopped for >12 months. These results show that pain-related grey matter volume decreases are present in individuals from the general population. The lack of morphometric anomalies in subjects with past pain supports recent evidence suggesting that pain-related grey matter changes are reversible after cessation of pain.

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IMAGES OF SPINE CARE

Vertebral body osteolysis after minimal-access transforaminal interbody fusion

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Presented is a 63-year-old female who previously underwent an L5–S1 fusion and developed suprajacent degeneration and radiculopathy. She underwent a minimal-access transforaminal lumbar interbody fusion with a Capstone cage filled with 6 mg of recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge inserted from the left side. She subsequently developed postoperative left lower extremity radiculitis that was refractory to narcotics and gabapentin several months after the surgery (Figs. 1–3).

Fig. 1. Axial computed tomographic image 6 months after surgery.

Fig. 2. Sagittal computed tomographic image demonstrating vertebral body osteolysis at 6 months postoperatively.

Fig. 3. Coronal computed tomographic image demonstrating vertebral body osteolysis at 6 months postoperatively.

Meetings Calendar

Canadian Orthopaedic Association Annual Meeting
> July 7–9, 2011
> St. John's, Newfoundland, Canada
> Contact: www.coa-aco.org

American Orthopaedic Society for Sports Medicine (AOSSM)
Annual Meeting
> July 7–10, 2011
> San Diego, CA
> Contact: www.sportsmed.org

18th International Meeting on Advanced Spine Techniques
(IMAST)
> July 13–16, 2011
> Copenhagen, Denmark
> Contact: www.srs.org/imast

NASS Coding Update
> **July 15–16, 2011**
> **San Diego, CA**
> **Contact: www.spine.org**

Southern Orthopaedic Association 28th Annual Meeting
> July 20–23, 2011
> Kohala Coast, Big Island, HI
> Contact: http://soaasn.org

Western Orthopaedic Association 75th Annual Meeting
> July 27–30, 2011
> Honolulu, HI
> Contact: http://woa-assn.org

South African Orthopaedic Association 57th Congress
> September 5–8, 2011
> Sun City, South Africa
> Contact: www.saoa.org.za

International Society of Orthopaedic Surgery and Traumatology
(SICOT) 25th Triennial World Congress
> September 6–9, 2011
> Prague, Czech Republic
> Contact: www.sicot.org

Scoliosis Research Society 46th Annual Meeting
> September 14–17, 2011
> Louisville, KY
> Contact: www.srs.org

American Association for the Surgery of Trauma 70th Annual
Meeting
> September 14–17, 2011
> Chicago, IL
> Contact: www.aast.org

Clinical Orthopaedic Society 99th Annual Meeting
> September 29–October 1, 2011
> Charleston, SC
> Contact: www.cosociety.org

Congress of Neurological Surgeons 61st Annual Meeting
> October 1–6, 2011
> Washington, D.C.
> Contact: www.cns.org

Australian Orthopaedic Association and New Zealand
Orthopaedic Association Annual Scientific Meeting
> October 9–14, 2011
> Rotorua, Australia
> Contact: www.aoa.org/au/Home.aspx or www.nzoa.org.nz

Orthopaedic Trauma Association 27th Annual Meeting
> October 12–15, 2011
> San Antonio, TX
> Contact: www.ota.org

5th World Congress on Controversies in Neurology (CONy)–Asia
Pacific
> October 13–16, 2011
> Beijing, China
> Contact: www.comtecmed.com/cony/2011

Spine Society of Europe (Eurospine) Annual Meeting
> October 19–21, 2011
> Milan, Italy
> Contact: www.eurospine.org/

NASS Coding Update
> **November 1–2, 2011**
> **Chicago, IL**
> **Contact: www.spine.org**

NASS 26th Annual Meeting
> **November 2–5, 2011**
> **Chicago, IL**
> **Contact: www.nassannualmeeting.org**

Cervical Spine Research Society 39th Annual Meeting
> December 7–10, 2011
> Scottsdale, AZ
> Contact: www.csrs.org